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REPRODUCTIVE HEALTH IN WOMEN WITH CHILDHOOD-ONSET TYPE 1 DIABETES IN FINLAND

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ACADEMIC DISSERTATION

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TERMS AND ABBREVIATIONS

df = Degrees of freedom

Fecundity – The capacity to have children

Fertility – Several meanings: one of them is the capacity to have children, but in this study the word is used to describe the observed number of children of a person

Hazard (intensity) = a quantity expressing conditional probability of an event in a short time interval, given the event has not happened before

Hazard ratio (HR) = ratio of the hazard rate in the index group and the reference (control) group

Hysterectomy – Surgical removal of the uterus (womb)

Macrosomia – Large birth weight

Oophorectomy – Surgical removal of both ovaries

Parity – The number of pregnancies of a woman resulting in childbirth

SD= standard deviation

SIR = ratio of the incidence rate in the index group and reference group, adjusting for age in the reference group. Can be stratified by sex.

T1D = type 1 diabetes

WHO = World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Sjöberg L, Pitkäniemi J, Haapala L, Kaaja R, Tuomilehto J.
Fertility in people with childhood-onset type 1 diabetes.
Diabetologia 2013; 56(1): 78–81.
- II Sjöberg L, Kaaja R, Gissler M, Tuomilehto J, Tiitinen A, Pitkäniemi J.
Termination of pregnancy and sterilisation in women with childhood-onset type 1 diabetes.
Diabetologia 2017; 60 (12): 2377–2383.
- III Sjöberg L, Pitkäniemi J, Harjutsalo V, Haapala L, Tiitinen A, Tuomilehto J, Kaaja R.
Menopause in women with type 1 diabetes.
Menopause 2011; 18(2): 158–163.
- IV Sjöberg L, He L, Kaaja R, Tuomilehto J, Pitkäniemi J.
Parity and mortality in cases of childhood-onset diabetes mellitus.
Diabetes Metabolism Research and Reviews 2016; 32(6): 607–614.

The publications are referred to in the text by their roman numerals.

ABSTRACT

The aim of this study was to explore the development of reproductive health issues in women with childhood-onset type 1 diabetes (T1D) in Finland in recent decades, based on a large population-based cohort.

The study cohort consists of 2327 women and two individually matched control persons without diabetes for each person in the cohort. The cohort is part of the DERI (Diabetes Epidemiology Research International) cohort that was established at the beginning of the 1980s and it consists of all Finnish persons who were diagnosed with T1D at the age of seventeen or under in 1965–1979. The control persons are age-, sex- and birth place-matched persons without diabetes. Three of the studies are register-based cohort studies that compare women with and without diabetes in regard to four topics: family size, rates of terminations of pregnancy and sterilisation, and parity-related mortality. Studies I and IV also include men, both from the DERI cohort ($n = 2819$) and from the control group. The fourth study was a questionnaire study on menopausal age and factors affecting it, involving part of the study cohort. The survey results regarding age at menopause of persons with T1D were compared with general population data.

The study women had fewer children than the controls without diabetes: the average number of children was lower in women with diabetes (1.1 [95% CI 1.03, 1.15]) than in women without diabetes (1.83 [95% CI 1.77, 1.87]), but in younger birth cohorts a significant trend was seen towards decreased differences between women with and without diabetes. There were significantly more terminations of pregnancy among women with diabetes (standardised incidence ratio [SIR] 1.67 [95% CI 1.51–1.86] compared with control women) and the indications for termination were different: maternal medical indications comprised 23.6% of terminations in the diabetes group and 0.3% in the women without diabetes. Sterilisations were more common (SIR 1.69 [95% CI 1.56–1.83] in the diabetes group and 22.9% them were carried out for maternal medical indications, the corresponding figure among the control women being 0.3%. The difference between women with and without type 1 diabetes regarding the frequency of sterilisation vanished around the year 2000.

Age at menopause was associated with the grade of complications of diabetes: the age-related occurrence of menopause was higher in women with severe microvascular complications, i.e., proliferative retinopathy or end-stage renal disease. The mean age at menopause was not lower than in the general population.

Mortality was lower in persons with children than in childless persons in our study, independent of sex and diabetes status, but the relationship between parity and mortality was different in men and women: in women with diabetes, having

even one child was associated with lower mortality from diabetes compared with childless women, whereas in men, the difference was seen only in men with two children or more.

The studies indicate that differences in reproductive issues between women with and without childhood-onset T1D have decreased over time. Compared with women without diabetes, parity has been lower and the frequencies of terminations of pregnancy and sterilisations have been higher in women with T1D than in the general population. There are differences in parity-related mortality between women and men with T1D; the underlying reasons and mechanisms are not clear. If pregnancy has a protective effect in women with T1D, this could partly be explained by the fact that women with diabetes learn to maintain good metabolic control during pregnancy and that they are also motivated to keep up this good control after giving birth.

A high quality of life is a central aim of good diabetes care. Future studies should focus on factors affecting the fecundity and fertility of women with diabetes and whether an improvement in fertility also improves prognosis and quality of life.

TIIVISTELMÄ

Tämän tutkimuksen tavoitteena oli selvittää tyypin 1 diabetesta lapsuudesta saakka sairastaneiden naisten lisääntymisterveyteen liittyviä tekijöitä viime vuosikymmenten aikana laajan väestöpohjaisen kohortin avulla.

Tutkimuskohorttiin kuuluu 2327 naista ja heidän yksilöllisesti poimitut verrokkihenkilönsä, jotka eivät sairasta diabetesta, kaksi verrokkiä kohortin jokaista naista kohti. Kohortti on osa kansainvälistä DERI-kohorttia ((Diabetes Epidemiology Research International), joka luotiin 1980-luvun alussa. Kohorttiin sisällytettiin kaikki Suomessa vuosina 1965–1979 syntyneet henkilöt, joilla todettiin tyypin 1 diabetes ennen 18 vuoden ikää. Verrokkit ovat iän, sukupuolen ja syntymäseudun suhteen kaltaistettuja henkilöitä, joilla ei ollut diabetesta. Kolme neljästä osatutkimuksesta on rekisteripohjaisia kohorttitutkimuksia, joissa diabetesta sairastavia naisia ja verrokkinaisia verrataan toisiinsa neljän eri tekijän suhteen: perhekoko, aborttien ja steriloinnin ilmaantuvuus sekä lapsilukuun suhteutettu kuolleisuus. Osatutkimuksiin I ja IV sisältyvät myös DERI-kohortin miehet (n=2819) ja heidän verrokkinsa. Neljäs osatyö oli vaihdevuosi-ikää ja siihen vaikuttavia seikkoja selvittävä kyselytutkimus, johon kutsuttiin osa DERI-kohortista. Kyselytutkimuksen tuloksia verrattiin väestötietoihin.

Diabetesta sairastavat naiset saivat vähemmän lapsia kuin verrokkit, jotka eivät sairasta diabetesta: lasten keskimääräinen lukumäärä oli alempi diabetesryhmässä (1,1 [95 % CI 1,03, 1,15]) kuin verrokkiryhmässä (1,83 [95 % CI 1,77, 1,87]), mutta nuorimmissa syntymäkohorteissa näkyi merkitsevä muutossuunta ryhmien välisen erojen vähenemiseen. Diabetesta sairastavilla naisilla oli merkitsevästi enemmän raskaudenkeskeytyksiä (standardoitu ilmaantuvuussuhde SIR 1,67 [95 % CI 1,51, 1,86] verrattuna verrokkinaisiin). Raskaudenkeskeytysten syyt olivat myös erilaiset: äidin terveyteen liittyvät syyt olivat taustalla 23,6 prosentissa kaikista diabetesta sairastavien naisten keskeytyksistä, kun taas verrokkiryhmässä vastaava osuus oli 0,3 %. Sterilointeja tehtiin enemmän diabetesta sairastaville naisille (SIR 1,69 [95 % CI 1,56, 1,83] ja niistä 22,9 % tehtiin terveyteen liittyvistä syistä; vastaava osuus verrokkiryhmässä oli 0,3 %. Ryhmien välinen ero sterilointien ilmaantuvuudessa katosi vuonna 2000.

Vaihdevuosi-ikä liittyi diabeteskomplikaatioiden asteeseen: ikään liittyvä vaihdevuosi-ilmaantuvuus oli korkeampi naisilla, joilla oli vaikeita mikrovaskulaarisia komplikaatioita, eli silmien verkkokalvojen uudissuonimuodostusta (proliferatiivista retinopatiaa) tai vakavia munuaismuutoksia. Keskimääräinen vaihdevuosi-ikä ei ollut alempi kuin väestössä yleensä.

Lapsettomien henkilöiden ikään suhteutettu kuolleisuus oli suurempi kuin lapsia saaneiden, riippumatta sukupuolesta tai diabeteksestä, mutta lapsiluvun ja

kuolleisuuden välinen suhde oli erilainen naisilla ja miehillä. Diabetesta sairastavilla naisilla jo yhden lapsen saaneiden naisten kuolleisuus oli alempi kuin lapsettomien naisten, kun taas miehillä ero ilmaantui vasta kahden lapsen kohdalla.

Tutkimus osoittaa, että diabetesta sairastavien ja sairastamattomien naisten väliset erot ovat vähentyneet ajan myötä. Diabetesta sairastamattomiin naisiin verrattuna diabetesta sairastavilla naisilla on ollut vähemmän lapsia, enemmän raskaudenkeskeytyksiä ja enemmän sterilisaatioita. Lapsiluvun suhde kuolleisuuteen on erilainen diabetesta sairastavilla naisilla kuin miehillä; tämän eron syitä ei tiedetä. Mikäli raskaudella on diabetesta sairastavaa naista suojaava vaikutus, se voi osittain liittyä siihen, että naiset oppivat raskausaikana saavuttamaan diabeteksen hyvän hoitotasapainon ja ovat motivoituneita ylläpitämään sitä myös synnytyksen jälkeen.

Hyvä elämänlaatu on diabeteksen hyvän hoidon keskeinen tavoite. Tulevat tutkimukset voisivat keskittyä hedelmällisyyteen ja lapsilukuun vaikuttaviin tekijöihin sekä selvittämään, parantaako lapsiluvun kasvu myös naisten ennustetta ja elämänlaatua.

SAMMANFATTNING

Syftet med denna studie var att beskriva hur reproduktionsrelaterade hälsofrågor hos kvinnor med typ 1-diabetes utvecklats i Finland under de senaste årtiondena, baserat på en omfattande populationsbaserad kohort.

Studiekohorten består av 2327 kvinnor och två individuellt utvalda kontrollpersoner utan diabetes för var och en av kohortpersonerna. Kohorten ingår i den internationella DERI-kohorten (Diabetes Epidemiology Research International), som grundades i början av 1980-talet. Kohorten omfattar alla finländare som fick diagnosen typ 1-diabetes före 18 års ålder under åren 1965–1979. Kontrollpersonerna är personer utan diabetes, som är individuellt matchade beträffande ålder, kön och födelseregion. Tre av delstudierna är registerbaserade kohortstudier som jämför kvinnor med och utan diabetes med avseende på fyra faktorer: barnantal, frekvensen av aborter och steriliseringar samt mortalitet i relation till barnantalet. Studierna I och IV inkluderar också män, både i DERI-kohorten ($n=2819$) och i kontrollgruppen. Den fjärde studien var en enkätstudie kring menopausåldern (övergångsåldern) och faktorer som påverkar den; denna studie omfattade en del av kohorten. I enkätstudien jämfördes resultaten med data från tidigare populationsbaserade studier.

Kvinnor med typ 1-diabetes fick färre barn än kvinnorna i kontrollgruppen: medelantalet barn var lägre hos kvinnorna med diabetes ($1,1$ [95 % CI $1,03, 1,15$]) än hos kontrollpersonerna utan diabetes ($1,83$ [95 % CI $1,77, 1,87$]), men i de yngre åldersgrupperna observerades en signifikant trend i riktning mot en minskad skillnad mellan grupperna. Bland kvinnorna med diabetes förekom signifikant fler avbrytanden av graviditeter (standardiserad incidenskvot [SIR] $1,67$ [95 % CI $1,51, 1,86$] jämfört med kvinnor i kontrollgruppen) och de bakomliggande grunderna för avbrytandena var olika: hälsoskäl hos modern utgjorde $23,6$ % av avbrytandena i gruppen med diabetes och $0,3$ % i kontrollgruppen. Steriliseringar var signifikant vanligare i gruppen med diabetes (SIR $1,69$ [95 % CI $1,56, 1,83$]) och $22,9$ % av dem utfördes av hälsoskäl, medan motsvarande andel bland kontrollgruppens kvinnor var $0,3$ %. Skillnaderna mellan grupperna beträffande steriliseringsfrekvens utjämnades kring år 2000.

Menopausåldern var associerad med graden av diabeteskomplikationer: menopausförekomsten i relation till åldern var högre hos dem som hade svåra mikrovaskulära komplikationer, dvs. proliferativ retinopati (ögonbottenförändringar med nybildning av blodkärl) och svår nefropati (diabetisk njursjukdom). Menopausåldern var i medeltal inte lägre än i den övriga befolkningen.

Mortaliteten i relation till ålder var lägre bland personer som hade barn jämfört med barnlösa personer, oberoende av kön och diabetesstatus. Förhållandet

mellan barnantal och mortalitet var olika bland kvinnor än bland män: bland kvinnor med diabetes var mortaliteten lägre bland kvinnor med minst ett barn än bland kvinnor utan barn, medan motsvarande skillnad bland män sågs enbart hos män med minst två barn.

Studien visar att skillnaderna i reproduktiv hälsa mellan kvinnor med och utan typ 1-diabetes har minskat med tiden. Kvinnor med typ 1-diabetes har fått färre barn samt genomgått fler aborter och steriliseringar än kvinnor i den övriga befolkningen. Förhållandet mellan barnantal och mortalitet vid typ 1-diabetes är olika bland kvinnor och män; de underliggande orsakerna är okända. Ifall graviditet har en skyddande effekt med tanke på livet efter graviditeten, kunde det delvis förklaras med att kvinnor med typ 1-diabetes lär sig upprätthålla en god diabeteskontroll under graviditeten och att de är motiverade att upprätthålla denna kontroll också efter förlossningen.

God livskvalitet är ett centralt mål för god diabetesvård. Framtida studier bör fokusera på faktorer som påverkar fruktsamheten och fertiliteten hos kvinnor med diabetes samt på huruvida en ökad fertilitet också förbättrar kvinnors prognos och livskvalitet.

1 INTRODUCTION

Type 1 diabetes (T1D), also called insulin-dependent diabetes mellitus, is a disease where the patients are dependent on externally administered insulin because of absolute or relative insufficiency of insulin. The incidence of T1D varies in different countries; Finland is the country with the highest incidence in the world (1); in 2015, 62.3/100 000/year (2). T1D has a large impact on the everyday lives of affected individuals and its effects are also reflected by lower life expectancy compared with that in the general population (3–5).

The impact of T1D on female reproductive health has not been greatly studied. According to the WHO, reproductive health “addresses the reproductive processes, functions and system at all stages of life” (6). Pubertal development, family planning, pregnancy, giving birth, infertility and menopause are all reproductive-health issues.

Recent trends in reproductive health in the general population in Finland are well documented and population-based registry data is regarded as very reliable (7–10). The incidence of terminations of pregnancy has decreased over the years and is lower than in the other Nordic countries (8.2/1000 women of fertile age in 2015) (11). The total fertility rate, defined as the number of children a woman would have during her lifetime if she survived until the end of her fertile years and gave birth to the average number of children specific for her country of residence, was 1.71 in 2014 in Finland, which was the second lowest figure in the Nordic countries. The total fertility rate is higher in the Nordic countries than in Europe in general. The rates of stillbirth, neonatal mortality and perinatal mortality in Finland are among the lowest in the world (12). Maternal mortality has been almost nonexistent since the start of the 1980s and the absolute number of maternal deaths varies between 1 and 7 per year (13). Sterilisation rates in Finland increased from the 1980s onwards and then decreased after 2000; the relative proportion of sterilisation procedures performed on women has decreased (14).

Among other things, questionnaire studies are needed to explore age at menarche, to distinguish between voluntary and involuntary infertility, and to establish menopausal age. In Finland, it has been estimated that the median menopausal age is 51 years (15).

Before 1922, when the use of insulin started in the treatment of persons with T1D, survival for more than two years after diagnosis was very rare and there are only very few records of observations on reproductive health from that era (16). Within a decade after the introduction of insulin treatment, it was noted that women with T1D differ from women in the general population in several ways regarding reproductive health. Many of these features are still considered

characteristic of women with T1D: later onset of pubertal development (16–18), irregular menstruation patterns (18,19), fewer children (19,20), more stillbirths (21), more adverse pregnancy outcomes (21,22), more birth defects in the offspring (23) and earlier menopause (24) than in the general population.

Much effort has gone towards preventing complications of diabetes, including those related to pregnancies of women with pre-pregnancy diabetes, i.e. pregnancy complications, stillbirths and birth defects. In 1989, representatives from all European countries and the World Health Organization agreed unanimously upon the Saint Vincent Declaration, which has several five-year targets within the framework of reduction of the burden of diabetes. One of these targets was to “achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman” (25). During the years that have passed since 1989, much progress has been made, but there are still significantly more pregnancy complications, stillbirths, and cases of perinatal mortality and birth defects related to pregnancy in women with T1D than in pregnancies in general (22), Finland included (26). Among pregnancy complications, those most commonly studied are pre-eclampsia, preterm delivery and macrosomia. According to the results of a Swedish study carried out in 2009, the risk of pre-eclampsia is more than fourfold, that of very preterm birth is threefold and that of foetal macrosomia more than tenfold in women with T1D compared with those in the general population (21). General population trends in Finland are also seen in women with T1D: obesity in pregnant women with T1D is increasing, which potentially can affect the complication profile (21,27).

Microvascular complications of diabetes, such as retinopathy and nephropathy, greatly impair the quality of life of persons with diabetes. Nephropathy is one of the main factors influencing morbidity and mortality in people with T1D (4). It has been estimated that diabetic nephropathy is present in 2.5–5% of pregnancies of women with T1D (28). Diabetic microangiopathy often progresses during pregnancy. (29) It is, however, unclear if the changes that appear during pregnancy are reversible or not. According to previous studies, the progression of microangiopathy is reversible in most cases, as regards both retinopathy and nephropathy, but the more severe the pre-pregnancy situation, the higher the risk of permanent progression (30,31). Since the pre-conceptional degree of both complications is considered to affect the risk of further progression of the angiopathies (32), pre-pregnancy counselling is particularly important when retinopathy or nephropathy is present before pregnancy.

This study was started in order to investigate whether the general improvements in reproductive health issues are reflected in the reproductive health of women with type 1 diabetes, and which factors are particularly associated with reproductive health in women with type 1 diabetes in the 21st century.

2 REVIEW OF THE LITERATURE

2.1 Features of type 1 diabetes and reproductive health

The most important factor influencing the effect of T1D on female reproductive health, including development of the foetus, is hyperglycaemia. The frequency of hyperglycaemic episodes during pre-pregnancy life after the diagnosis of diabetes and during pregnancy is important; the more hyperglycaemic periods during pregnancy, the higher the risks of congenital anomalies and spontaneous abortion (33,34). The occurrence of diabetic complications, i.e. nephropathy, retinopathy, neuropathy and macroangiopathies, also influences family-planning decisions and family size.

Poor metabolic control during the first trimester of pregnancy significantly increases the risks of stillbirth and birth defects (23,35), and it also increases the risk of spontaneous abortion (34). Hyperglycaemia affects several biochemical pathways during foetal development (33,36) and is regarded as the main factor causing the above-mentioned pregnancy-related problems in women with T1D.

In the last trimester of pregnancy, metabolic control also affects professionals' decisions on mode and timing of delivery, at least indirectly, as hyperglycaemia in the second and third trimester of pregnancy is considered one of the main aetiological factors behind foetal macrosomia (27,28), and macrosomia is one of the main indications for Caesarean section in women with T1D (37,38).-

2.2 Fertility in women with childhood-onset type 1 diabetes

The word "fertility" is used in several ways in the literature. Most commonly, fertility is defined as the capacity to reproduce. In our study, the term fertility is used in its demographic meaning and it is estimated by the average observed number of offspring of a person. To describe the capacity to produce offspring, the more specific word "fecundity" is used, a word that cannot be misinterpreted.

Women with T1D tend to have fewer children on average than women in the general population (20,39,40). There are, though, very few studies that have clearly shown that the fecundity of women with T1D is lower than that of other women (41,42), although there are potential mechanisms by which that could be the fact. The fertile period of life has generally been considered to be shorter in women with T1D because of delayed menarche (18) and premature menopause (24).

Table 1 shows previous studies on this topic. Three of them, one from Japan, one from France and one from Germany, were hospital-based. Two of them were

focused on marital status and number of offspring in persons with T1D (40,43). The Japanese investigators compared the number of offspring with general-population data obtained through an earlier survey (40), whereas the French study concerned only comparison between women and men with T1D (43). The third study was a German cross-sectional study from 2012 (39), where the main finding was that persons with T1D had fewer children than the background population. Jonasson et al. (20) carried out a large register study in Sweden. They found that women with T1D had fewer children than the general population and, furthermore, they detected a decreasing difference compared with the general population. In more recent birth cohorts, the number of children approached that of other women. This particularly concerned women who had uncomplicated diabetes.

There are two previous studies that have been carried out in an attempt to explore the extent to which women with T1D want to restrict their family size because of diabetes. Neither of these studies is recent (19,44). In an American study from 1985, there were 37 women who had been diagnosed with T1D before the age of 20; eleven of them (30%) had decided not to have children because of their diabetes (44). In a Danish study from 1992, more than half of the respondents (111/197) with diabetes reported that having the condition influenced their attitude towards having children. The proportions of women with involuntary infertility did not differ between women with and without diabetes. (19)

Table 1. Studies related to the number of offspring in women with T1D.

Reference	Aim	Study design	N	Results
Aono et al. 2000 Japan (40)	To investigate the lifestyle and social circumstances of persons with T1D. Marriage status and number of children were included.	Hospital-based questionnaire study. Comparison with general-population data obtained via an earlier nationwide survey.	659 women with T1D	54.7% of the women with T1D had no children, 37.5% had one child, 7.8% had two and none had more than two children.
Sobngwi et al. 2003 France (43)	To compare marital status, number of offspring and incidence of T1D in the offspring, between men and women with T1D	Hospital-based: data from patient records and patient interviews	78 women with T1D	35% of the women had no offspring (corresponding figure for men: 8%), 43% of women (and 61% of men) had two or more offspring. No comparison with persons without diabetes.
Jonasson et al. 2007 Sweden (20)	To assess fertility in women with T1D and the risk of congenital anomalies in their offspring	Nationwide register study covering 1965–2004	5978 women with T1D	The standardised fertility rate (observed number of births / expected number of births) varied between 0.63 and 0.82 and was higher in more recent birth cohorts.
Holstein et al. 2012 Germany (39)	To assess the number and sex ratio of offspring of persons with T1D	Regional cross-sectional study, comparison with background population	364 women with T1D	Ages 18–49: fertility rate 0.88 in women with T1D, 1.36 in women without T1D. Ages 41–45: 36.2% of women with T1D were childless (and 20% of women without T1D).

2.3 Termination of pregnancy and type 1 diabetes

Women with T1D have been advised to use efficient contraceptive methods ever since it became evident that there are many risks involved for a woman with T1D and her offspring, especially if conception occurs when the blood glucose control of the mother is not optimal. The strongest efforts to prevent adverse effects in the offspring have been focused on preventing women with diabetes from having any children at all (45). To date, experts have agreed that women with diabetes and coronary heart disease should not get pregnant, which is considered important mainly for the prognosis of the mother; neither should those with severe nephropathy or retinopathy (46).

In earlier days, if a woman with T1D and suboptimal glucose control became pregnant she was often advised to undergo termination. This was practiced in Finland in the 1970s, although there was no official national or international consensus on the circumstances under which and at what gestational stage a pregnancy should be terminated (47). There are some previous studies (Table 2) on the incidence of termination of pregnancy among women with T1D in Europe. They all show that termination of pregnancy is more frequent among women with T1D (48–52) and that a larger proportion of these terminations have maternal medical indications than those performed among all women (51,52). Many of the previous studies lack information on indications for termination of pregnancy.

Table 2. Studies on termination of pregnancy in women with type 1 diabetes.

Reference	Aim	Study design	N	Results	Termination indications
Nielsen et al. 1993 Denmark (52)	To describe the outcome of all pregnancies among T1D women	Retrospective, hospital-based study in a geographically defined area during a 15-year period	205 women, 328 pregnancies	Pregnancy terminations: 12.5% of all pregnancies	Maternal medical reasons: 24% of all terminations (other indications not stated)
Casson et al. 1997 England (49)	To monitor pregnancies among T1D women for pregnancy loss, foetal growth and congenital malformation	Hospital-based population cohort study in a geographically defined area over five years	355 women, 462 pregnancies	Pregnancy terminations: 5.2% of all pregnancies	No data on maternal medical indications. Foetal medical indications: 37.5%
Lorenzen et al. 1999 Denmark (50)	To describe the pattern of miscarriage and stillbirths in women with T1D	Population-based questionnaire study in a geographically defined area; general response rate: 84%, response rate to termination-related questions: 78%	1218 women, 1285 offspring	Pregnancy terminations: 17.9% of all pregnancies	No data on indications
Penney et al. 2003 Scotland (51)	To determine pregnancy outcome in women with T1D	Prospective, hospital-based study over a one-year period	273 women and pregnancies	Pregnancy terminations: 7.3% of all pregnancies	30% of terminations: foetal medical indications, 70%: socioeconomic indications
McGrogan et al. 2014 United Kingdom (48)	To investigate pregnancy losses in T1D and T2D women	Retrospective study utilizing primary-care records during a 14-year period in a geographically defined area	548 women with T1D, 667 pregnancies	Pregnancy terminations: 9.1% of all pregnancies	67% for non-medical reasons; no data on maternal versus foetal medical indications

2.4 Type 1 diabetes and female sterilisation

Sterilisation was considered the most reliable contraception method before hormonal intrauterine contraceptive devices were introduced. There are previous studies that have shown that sterilisation procedures are more common among women with T1D than among women without diabetes: 23% vs. 10% according to a Danish study (53), and 5.8% vs. 3.7% of women in a British study (54) used sterilisation as contraceptive method. In 1978, a group of American opinion leaders in the social and medical field published a text directed to young people with diabetes, and their doctors, stating that women with diabetes who were older than thirty-five, women who had had diabetes for more than twenty years and women with serious diabetic vascular complications should strongly consider sterilisation (55).

After the arrival of hormonal intrauterine devices (IUDs), the rate of sterilisation declined in Finland (14). The present study does not include any data on the use of such IUDs among women with T1D – neither are there any previous data on sterilisations performed among Finnish women with T1D.

2.5 Pregnancy and type 1 diabetes

Although much effort has been directed to reducing factors related to the elevated risks associated with childbearing in women with T1D, there are still pregnancy complications that are far more common in this group of women: preterm delivery, intrauterine growth retardation, pre-eclampsia, stillbirth, perinatal death, congenital anomalies and high birth weight of the offspring (22). Poor metabolic control and diabetic nephropathy in early pregnancy increase the risk of all adverse outcomes of pregnancy (22,28). The accumulation of factors related to the pregnancy-related risks influence individual decisions on family size (19).

2.6 Menopausal age in women with type 1 diabetes

Menopause marks the end of the fertile period of a woman's life. Menopause is defined as the cessation of menstruation, but menopausal age cannot be defined before one year has passed without menstrual bleeding, i.e. retrospectively (56). The timing of menopause matters: early menopause has in some studies been associated with a higher risk of coronary heart disease and a higher mortality rate (57).

Women with T1D are at a higher risk of cardiovascular disease than other women (58). Early menopause is considered a cardiovascular risk *per se* (57) – or, on the other hand, some claim that an unfavourable cardiovascular risk profile, as

seen in T1D, brings menopause forward (59). These factors contribute to the fact that menopausal age matters, especially for women with T1D.

Studies on menopausal age in women with T1D are listed in Table 3. The first study on menopausal age in women with diabetes who had received insulin therapy was published in Sweden in 1954: Bergqvist collected information on 37 women who were 45 years or older at the time of the study and with diabetes onset between 18 and 44 years of age. There were 19 women in this study who reported that their menstruation had stopped, at the average age of 47.9 years. There were ten women over 45 years of age who were still premenopausal (60). At that time, the differentiation of diabetes mellitus into type 1 and type 2 was not yet well established – although the fundamental study on this had been published as early as 1936 (61) – and both the study by Bergqvist and its referenced studies included persons some of whom, on the basis of descriptions, would nowadays be defined as having type 2 diabetes. The conclusions of that report were that menopause occurs slightly earlier in women with diabetes than in the general population, but the author remarked that conclusions should be made with caution.

The next study on menopausal age in women with T1D was published in 2001 by Dorman et al. (24). In their study, there was a statistically significant difference in menopausal age between women with T1D and the control women without diabetes, of whom half were sisters of the women with diabetes.

The participants in Dorman's study were diagnosed with insulin-dependent diabetes at the age of 17 or under in 1950–1964 and recruitment to the study was hospital-based. Of the women who were contacted, 71% responded. Their parents and siblings were asked to participate as control persons, as were population controls from the same geographical regions as the study persons. The participants were 143 study persons with diabetes, 186 sisters without diabetes and 160 population controls. The women with diabetes differed significantly from those without diabetes in the following baseline characteristics: the women with diabetes had more autoimmune thyroiditis, they were older at menarche, had more menstrual irregularities at under 30 years of age, had not used oral contraceptives to the same extent, had fewer children, and had lower BMI and lower yearly income. When exploring age at menopause, T1D was the most significant risk factor of early menopause; others were being nulliparous, having had menstrual irregularities at under 30 years of age and having had unilateral oophorectomy. Menopausal age among women with T1D was 41.6 years; 8.3 years earlier compared with their sisters and 6.4 years earlier compared with other controls.

In another American study (62), women with diabetes reported a mean menopausal age of 44 years, compared with 50 years in those without diabetes. There were 29 participants with diabetes who had reached menopause. The objective of this study was to explore the association between coronary artery calcium and menstrual dysfunction on the one hand, and birth control use on the

other hand, and the difference in the mean menopausal ages was an incidental finding. The classification of diabetes into type 1 and type 2 was not necessarily correct in all cases, a fact pointed out by the authors.

The other two studies published on this subject support the interpretation that menopausal age in women with T1D does not differ from that in the general population (63,64). In a Dutch study published in 2015, women with diabetes were recruited through several hospitals and the national diabetes society. The control persons without diabetes were part of an existing study cohort. There was no significant difference in menopausal age between women with and without diabetes (64). No data on diabetes complications was available. The other study on this topic, carried out after our study, is from the United States, by Kim et al. Its main purpose was to compare two different kinds of diabetes treatment in relation to the incidence of menopause. Age at menopause did not significantly differ between the groups; it was 49.9 and 49.0 years, respectively, in the intensive treatment group versus the conventional treatment group (63). In this study, there was no association between menopausal status and autoimmune disease or severe microvascular complications; in fact, there were very few participants with severe retinopathy or nephropathy. There is a recent study carried out in the same centre as the study mentioned above, the main purpose of which was to explore a possible association between markers of ovarian ageing, vascular health and diabetes. The investigators found no significant difference in Anti-Müllerian hormone levels, which are considered a marker of ovarian ageing, between women with and without T1D. The participants were relatively young, which might have influenced the results (65).

There are two main hypotheses regarding the possible mechanisms of early menopause in women with T1D: that it results from autoimmune mechanisms or that it has a vascular aetiology. An autoimmune aetiology is supported by the fact that anti-ovarian antibodies are often seen both in premature ovarian failure and in autoimmune diseases, including T1D (66,67).

Table 3. Studies related to menopausal age in women with type 1 diabetes.

Reference	Aim of the study	Study design	Number of study persons	Results regarding reproductive factors
Bergqvist 1954 Sweden (60)	To evaluate the gonadal function of women with diabetes	Clinical study	37	Menopause occurs "slightly earlier" in women with diabetes
Dorman et al. 2001 USA (24)	To study menopausal age and factors associated with it in women with type 1 diabetes compared with their sisters and population controls without diabetes	Hospital-based study on women with T1D; siblings and geographically matched persons as controls	143 + 186 + 160	Menopause occurs earlier in women with T1D – the reproductive life span in women with T1D is 6 years shorter
Snell-Bergeon et al. 2008 USA (62)	To determine which factors influence the development of coronary artery disease in persons with type 1 diabetes	Clinical case-control study	293 women with T1D, 319 women without	Menopausal age: T1D 44 ± 13 (SD) years, control women 50 ± 4 years
Kim et al. 2014 USA (63)	To determine the impact of intensive versus conventional T1D treatment on menopause	Randomized controlled trial	652 (follow-up: 564)	Menopausal age: 49.9 years (intensive treatment), 49.0 years (conventional treatment)
Yarde et al. 2015 Netherlands (64)	To determine whether menopause occurs earlier in women with T1D	Cross-sectional study (questionnaire) directed to postmenopausal women	140 women with T1D, 5426 women without	Menopausal age: 49.8 ± 4.7 (SD) years in women with T1D, 49.8 ± 4.1 years in women without T1D

2.7 The relationship between parity and mortality: does type 1 diabetes modify it?

In many studies carried out through the years and in different settings, an association between parity and mortality has been detected, both in men and in women (68–70). Mortality is higher in persons without children, and in many studies, mortality is lowest in persons with two children. The reasons for this are not clear. One of the possible mechanisms might be selection bias due to an association between an unhealthy lifestyle and childlessness. Selection bias means that persons who have poor general health more often remain childless – because of their own choice or even because of difficulties in finding a partner. When looking at persons with a longstanding chronic disease, there may be additional factors that influence both finding a partner and decisions regarding childbirth, e.g. concern about transmitting the disease to the children and concern about progress of the disease (19).

Type 1 diabetes is associated with a higher mortality rate compared with that in the general population (5,71). Children of persons with T1D have a strongly elevated risk of acquiring the disease (72,73). These facts might affect decisions on birth control, but studies exploring this topic are scarce (19).

2.8 Previous studies involving the cohort

The cohort involved in this study was initially created to investigate mortality among persons with childhood-onset T1D in four countries: Finland, Israel, Japan and the USA (one region in the US). The cohort was named DERI, which stands for Diabetes Epidemiology Research International. The cohort is described in more detail in Section 4.1.

There have been many publications on mortality in the international DERI cohort in various countries (74–77), including comparison of mortality differences between countries (78–83). Ten years after the DERI cohort was created, mortality differences between countries were evaluated. Overall mortality was higher in Japan than in Finland or Israel (81) and renal disease turned out to be a major factor behind the excess mortality in Japan (78). Suicide was most frequent in Finland (81). Violent deaths among male persons with T1D were more frequent in Finland and the USA than in Japan or Israel (79). In Finland, there was a greater sex difference in mortality than in the other countries, males having a significantly higher mortality rate than women (79).

3 AIMS OF THE STUDY

This mainly register-based study is focused on the reproductive health of Finnish women with childhood-onset type 1 diabetes mellitus compared with population-based control women without diabetes. The specific aims addressed in the four studies were to explore:

1. Fertility and family size of women with type 1 diabetes
2. The prevalence rates of termination of pregnancy and sterilisation in women with type 1 diabetes
3. Age at menopause in women with type 1 diabetes
4. Mortality in women with type 1 diabetes in relation to family size.

4 MATERIAL AND METHODS

This study is based on data on Finnish women diagnosed with childhood-onset type 1 diabetes in 1965–1979. Three of the included studies are retrospective and register-based; one is a cross-sectional survey. In two of the four articles included in this study, Studies I and IV, men are also included. They belong to the same cohort as the women. This thesis is focused on women; some comparisons are made with men in the cohort, when relevant from the viewpoint of reproductive health.

4.1 Presentation of the study cohort

The international Diabetes Epidemiology Research International (DERI) cohort was established to study mortality among those with childhood-onset T1D in population-based cohorts in Finland, Israel, Japan and the United States. The Finnish DERI cohort was established at the beginning of the 1980s. The persons in the DERI study were diagnosed with T1D at 18 years of age or under in 1965–1979 and placed on insulin at diagnosis. In the nationwide register, 5,166 Finnish cases were identified. Identification of the persons in the cohort has been considered to be virtually complete. Details regarding the identification are described in a thesis published in 1993 (84). The thesis itself concerns a cohort comprising more individuals than the established DERI cohort used in this study; the Finnish DERI cohort was defined in line with the international DERI cohorts, as described above, the essential characteristics being age at onset and date of diagnosis of T1D.

In Finland, a control group for the DERI cohort was established in the 1980s from the national database on reimbursement of drug costs for diabetes, located at the Social Insurance Institution. From the National Population Register, two control persons for each person with diabetes in the cohort were identified. They were matched for birth year, geographical birth region and gender. All control persons who had been discharged from hospital with a diagnosis of diabetes mellitus (data from the Hospital Discharge Register [HDR]) or who had offspring with a spouse with diabetes (data from the Population Register Centre) were excluded. Persons with Down's syndrome (data from the HDR) were also excluded from both the group of persons with diabetes and from the control group. The control group was established during collaboration between the National Institute of Health (renamed in 2009 as the National Institute of Health and Welfare) and The Social Insurance Institution of Finland. Data on the control group was utilized in Studies I, II and IV. The control group has so far not been utilized in any other studies than this.

For this study, people who died before the age of 14 were also excluded, since the study deals with reproduction, which is highly unlikely before the age of 14. After all exclusions, the data contains information on 2307 women with diabetes and 4530 women without diabetes.

4.2 Register data

In Studies I, II and IV, data from the following sources were used:

1. The Social Insurance Institution of Finland
2. The Hospital Discharge Register of the National Institute for Health and Welfare
3. The Population Register Centre
4. The Medical Birth Register (BR) of the National Institute for Health and Welfare
5. The Register on Induced Abortions
6. The Register on Sterilisations
7. Statistics Finland

When the cohort was established and when the control persons were selected, the Social Insurance Institution of Finland provided data on medication reimbursement: persons who had applied for reimbursement of costs arising from insulin treatment of T1D and who were under 18 years of age on the day of diagnosis were included in the cohort.

The Hospital Discharge Register (HDR) was utilized when exploring the number of live births (Studies I and IV), the number of terminations of pregnancy and sterilisations (Study II), and causes of death (Study IV). The Population Register provided us with data that links parents and offspring (Studies I and IV). The Medical Birth Register (BR) formed the basis of Study II, as did the Registers on Induced Abortions and Sterilisations. For Study IV, information on causes of death was provided by Statistics Finland.

4.3 Questionnaire survey

The data presented in Study III were obtained by way of postal questionnaires that were sent to women in the DERI cohort who were born before 1963. The year 1963 was selected because women born after that were considered unlikely to have reached menopause in 2002, when the study started. The first set of the

first round of questionnaires (n = 50) was sent in October 2002. The first set was also used as a pilot study, after which the questionnaire was evaluated and minor changes were made. The first round was completed by the end of 2003. Looking at the replies in the first round, it was evident that so few persons had reached menopause that the second round had to be postponed until three years had passed, in order to obtain more end points in the study.

In Study III, comparison was made with general population data based on previous population surveys.

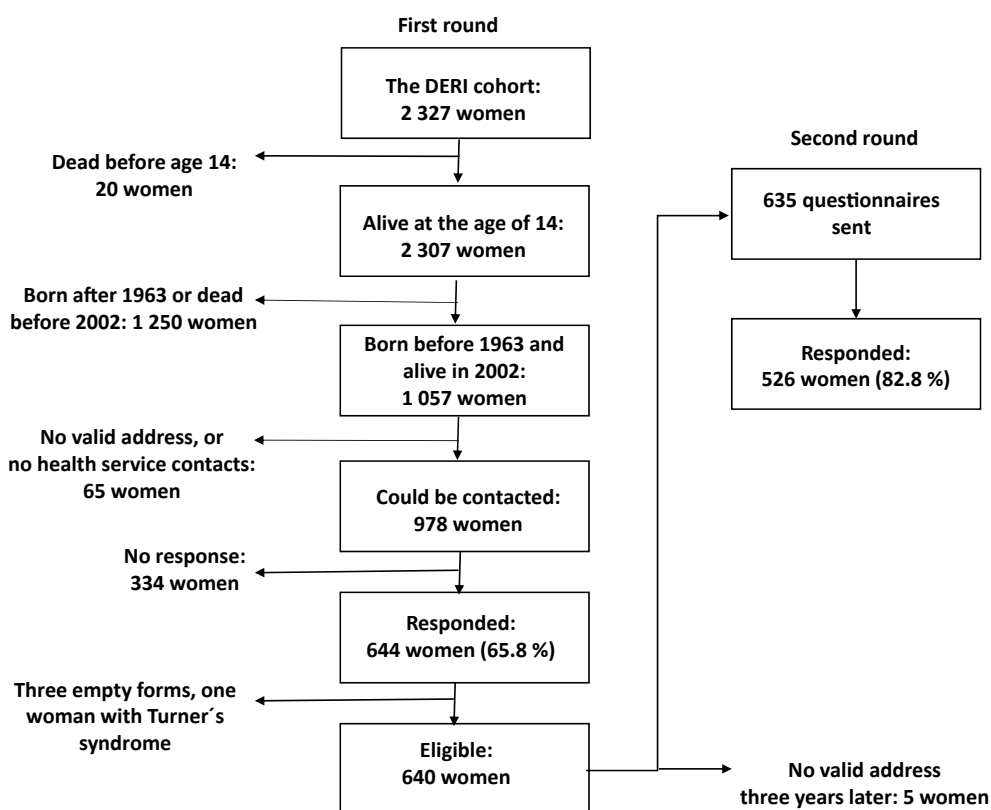


Figure 1. Flow chart of Study III.

The response rate in the first round was 65.8%. Three women returned an empty form and one woman had Turner's syndrome, leaving 640 eligible women. In the second round, questionnaires were posted to those who had replied in the first round. Excluding those who had died after the first round and those who could not be reached because of lack of a valid address, 635 questionnaires were posted. The response rate in the second round was 82.8%; 526 completed questionnaires were returned.

4.3.1 Assessment of menopause

The menopausal status of the respondents was defined mainly on the basis of their reply to the question “Do you still menstruate?” There were also questions on the menstrual cycle, contraception, hormonal therapy, surgical procedures and menopausal symptoms, to specify the individual situation of each respondent.

4.3.2 Non-response and non-consent

According to Finnish research ethics rules, study persons cannot be contacted on the basis of knowledge that a person has a certain disease according to a register. The heads of the hospital districts where the study persons lived were contacted and asked for permission to contact potential study persons. Covering letters were signed by both the director of the hospital district and our principal investigator. Permission to send questionnaires was not obtained for all study persons. Twelve persons had not had any recent hospital visits and could therefore not be contacted. Another 53 could not be reached because of lack of a valid address. Up to two reminders were sent to non-respondents in both rounds.

4.4 Ethical considerations

All studies followed University of Helsinki guidelines. Studies I, II and IV were approved by the ethics committees of the Department of Public Health at the University of Helsinki, and the Finnish National Institute of Health and Welfare. Study III was approved by the ethics committees of the Finnish National Institute of Health and Welfare and the Hospital District of Helsinki and Uusimaa.

In every step of the studies, effort has been made not to reveal the identities of the study persons, since the data contains information that can be interpreted as being very sensitive. All researchers involved have acted according to the data protection principles and the ethics rules of the University of Helsinki and the National Institute for Health and Welfare.

4.5 Design and statistical methods

Table 4 shows designs, aims, primary outcomes and comparisons connected with each article or manuscript.

In **Study I**, fertility (rate) was estimated as the average number of children born to a woman during the follow-up period per person. Follow-up started at the age of 14 and ended on December 31st, 2007, at the age of 50 or at death, whichever occurred first.

Confidence intervals for the fertility estimates were obtained by using the bootstrap method. Pearson's χ^2 test was utilized to compare the attained family sizes between women with and without diabetes.

The fitted multistate intensity models consisted of six states for persons with T1D and persons without the disease: alive (no children), dead, first child, second child, third child and fourth child. Either parental age or calendar date was chosen for the time scale in this intensity model. Rates and 95% exact Poisson confidence intervals of having children among women with and without diabetes are reported together with hazard ratios (HRs), 95% confidence intervals and Wald test p-values between women with and without diabetes as regards first, second, third and fourth children, using stratified proportional hazard models by case-control pairs. The interactions between the categorical birth cohort variable proportional hazards model and T1D status were estimated.

Table 4. Methodological aspects of the four studies.

Article	Aim	Design	Outcome	Comparison
I	Evaluate fertility	Retrospective cohort	Live birth of child	Fertility among T1D women versus fertility among non-T1D women (controls)
I	Evaluate attained family size	Retrospective cohort	Attained number of live offspring	Attained family size among T1D women versus attained family size among non-T1D women (controls)
I	Explore the intensity of having children	Retrospective cohort	Intensity of first, second, third etc. child	Intensity ratio (HR) = intensity (T1D) / intensity (controls)
II	Explore the association between T1D and terminations of pregnancy	Retrospective cohort	Intensity of termination of pregnancy	Intensity ratio (HR) = intensity (T1D) / intensity (controls)
II	Explore the association between T1D and sterilisation	Retrospective cohort	Intensity of sterilisation	Intensity ratio (HR) = intensity (T1D) / intensity (controls)
III	Evaluate average age at menopause	Cross-sectional study (survey)	Median age at menopause	Median age at menopause in T1D women included in the study, median age at menopause in Finnish women according to a population survey (15)
III	Evaluate prevalence of diabetic complications and autoimmune co-morbidity	Cross-sectional study (survey)	Prevalence of diabetic complications and autoimmune co-morbidity	Prevalence ratio (PR) = ratio of age-related prevalence of menopause among women with and without diabetic complications or autoimmune co-morbidity
IV	Evaluate the effect of parity on mortality	Retrospective cohort	Mortality by parity	Mortality ratio in women with and without T1D by parity (homogeneity of mortality ratios)
IV	Evaluate the effect of parity on cause-specific mortality	Retrospective cohort	Cause-specific mortality by parity	Cause-specific mortality ratio in women with and without T1D by parity (homogeneity of mortality ratios)

The main outcomes of **Study II** were termination of pregnancy, and sterilisation. Follow-up started on January the 1st, 1987, the date when the Birth Register was established, and ended either at the time of sterilisation, at the age of 50, at death or at the end of follow-up (Dec. 31st, 2011), whichever occurred first. The risks of termination of pregnancy and sterilisation were explored by age and calendar time period. Because of the known excess mortality among persons with T1D, competing risk methods were used for estimating the cumulative incidence of sterilisation. When estimating the risk of termination of pregnancy, follow-up started at the estimated time of conception and ended at either the time of birth of a child or the time of termination. Standardized incidence ratios (SIRs) were estimated using reference rates from women without T1D and the obtained 95% confidence interval (CI) using standard Poisson regression in order to adjust for both age and calendar time differences in intensities of termination of pregnancy and of sterilisation.

Time of menopause was the outcome measure in **Study III**. To investigate factors associated with the outcome among women in the DERI cohort, both cross-sectional and retrospective epidemiological cohort study designs were applied.

When it was unclear – based on the survey – whether or not the exposure (parity, smoking, autoimmune disease, hypertension, coronary heart disease, neuropathy, intermittent claudication, nephropathy or retinopathy, all listed in Table 6) occurred before the outcome (menopause), a cross-sectional design was utilized, and the association between exposure and outcome was expressed by prevalence ratios (PRs). The prevalence ratios were estimated by using a generalized linear model. A dichotomous outcome (0 = no menopause, 1 = menopause) was assumed to be Poisson-distributed (with log-link function). As the prevalence of menopause was more than 10%, variances of PRs and 95% confidence intervals were obtained using sandwich estimators.

For two of the variables, age at diagnosis and age at menarche, a retrospective cohort design was applied. The pair of observations in the analysis were the age at menopause on the one hand, and an indicator of the age-related occurrence of menopause (based on the survey) on the other hand. If menopause had not occurred by the time of the questionnaire survey, a person was censored. The association between age at diagnosis of diabetes (or age at menarche) on the one hand and age at menopause on the other hand was analysed by using standard methods of time-to-event analysis: the Kaplan–Meier method was used to obtain estimates of cumulative probability of menopause and the proportional hazards (Cox) model was used for the assessment of risk factors associated with menopause.

In **Study IV**, the primary outcomes were all-cause and cause-specific mortality. Follow-up started at the age of 14 and ended on December the 31st, 2010 or at death, whichever occurred first. The number of live-born children during follow-up and the date of birth of each child were also recorded for each study person. The three

most common groups of causes of death were diabetes-related deaths, deaths from cardiovascular diseases and deaths from accidents, violence and suicides. For these, cause-specific risks were estimated. In the control group there were naturally no diabetes-related deaths and among the persons without diabetes, only deaths from cardiovascular disease and accidents/violence/suicides were assessed.

The data was stratified on the basis of case-control status, sex, and the number of offspring (categories: 0, 1, 2, 3 or more). Crude mortality rates and 95% CIs for mortality rates were estimated and the observed numbers of deaths were assumed to be Poisson-distributed. We also adjusted for different age distributions with respect to number of children by estimating age-adjusted standardized mortality ratios (SMRs) and their 95% CIs for both sexes compared with their matched controls without diabetes.

A multi-state model with time-dependent covariates was used to analyse intermediate events (birth of children) (85). Parity can in this context be considered an internal time-dependent covariate, because many factors affect personal decisions regarding family size. Parity is related to a phenomenon often referred to as reverse causation (86), which means that it is unclear whether low parity increases the risk of death or if the increased risk of death causes lower parity. Parity can only be estimated for persons who are alive (87) and therefore the risk of mortality was explored by using a multi-state model.

We had to account for parity in the stratified analysis when we explored whether age at onset of T1D was associated with mortality. Because the persons with later onset of T1D in our study cohort were older (belonged to earlier birth cohorts) and thus had a higher expected mortality rate, we accounted for the effect of age by modelling the baseline mortality rate within a two-year interval of age.

Cause-specific mortality was estimated for the three most common groups of causes of death (diabetes-related deaths, deaths from cardiovascular diseases and deaths from accidents, violence and suicides) by diabetes status and the number of children, utilizing competing risk analysis (87). All analyses were performed by using R statistics and the mstate package for multi-state frameworks (88).

5 RESULTS

5.1 Fertility and family size

Family size attained during follow-up was significantly smaller among women with T1D (average number of children 1.15) than among control women (1.83) in our study. Table 5 shows (cohort-wise) the number of children born to women with T1D and controls. Many women in the earlier birth cohorts have reached menopause and thus their follow-up is complete regarding family size. Although women in later birth cohorts are still at reproductive age, the difference between women with and without T1D in the average number of children is roughly the same as in earlier cohorts.

Table 5. Number of women with and without type 1 diabetes and their live-born children during follow-up, by birth cohort. This is a descriptive table not aimed at testing the difference between women with and without diabetes.

Birth cohort	Number of women with T1D	Number of women without T1D	Number of children, mothers with T1D	Average number of children to mothers with T1D	Number of children, mothers without T1D	Average number of children to mothers without T1D
1947–1954	240	475	252	1.05	851	1.79
1955–1959	533	1052	598	1.12	2010	1.91
1960–1964	687	1361	856	1.25	2681	1.97
1965–1969	552	1088	648	1.17	1938	1.78
1970–1979	269	533	276	1.03	797	1.50
Sum	2281	4509	2630	1.15	8277	1.83

The attained family size was statistically significantly smaller among women with T1D than among control women; Pearson's χ^2 -test in comparison of attained family sizes in the two groups: $\chi^2 = 497.7$, $df = 4$, $p < 2.2 \times 10^{-16}$.

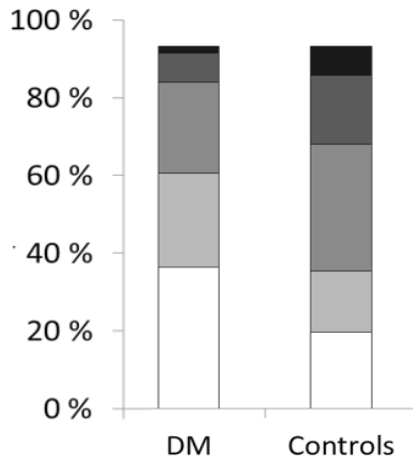


Figure 2. Attained family sizes in women with and without diabetes. White shading: no children, light grey: one child, mid-grey: two children, dark grey: three children, black: four or more children.

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To analyse the association between age at onset of T1D and fertility, we chose the study persons who were born in 1957–1965 (half of the women in the cohort), because those birth years include women from all categories of ages at onset (0–17 years). In these women, later age at onset of T1D was associated with a higher probability of having a second child (trend test of hazard ratios: $p = 0.002$; homogeneity test of hazard ratios: $p = 0.04$).

The study persons were divided into birth cohorts (birth years 1947–1955, 1956–1960, 1961–1964, 1965–1969 and 1970–1979) and the hazard ratios of having a first child were explored. The difference between women with and without T1D was smaller in more recent birth cohorts (homogeneity test of hazard ratios between birth cohorts: $p = 0.04$).

5.2 Terminations of pregnancy and sterilisation

The main finding in **Study II** was that both terminations of pregnancy and sterilisation were more common in women with diabetes than in control women.

During the 25-year follow-up, there were more terminations of pregnancy among women with T1D than among control women: the standardized incidence ratio (SIR) in comparison of the termination incidences in the groups was 1.67 (95% CI 1.51–1.86). Among the women with T1D, 17.1% of pregnancies were terminated; the corresponding figure among control women was 11.5%. These figures represent the proportion of pregnancies being terminated among pregnancies ending in

either childbirth or termination, since there was no data on spontaneous abortions. During our 25-year follow-up, approximately 25% of women with diabetes and 20% of women without diabetes who experienced a pregnancy had at least one termination of pregnancy.

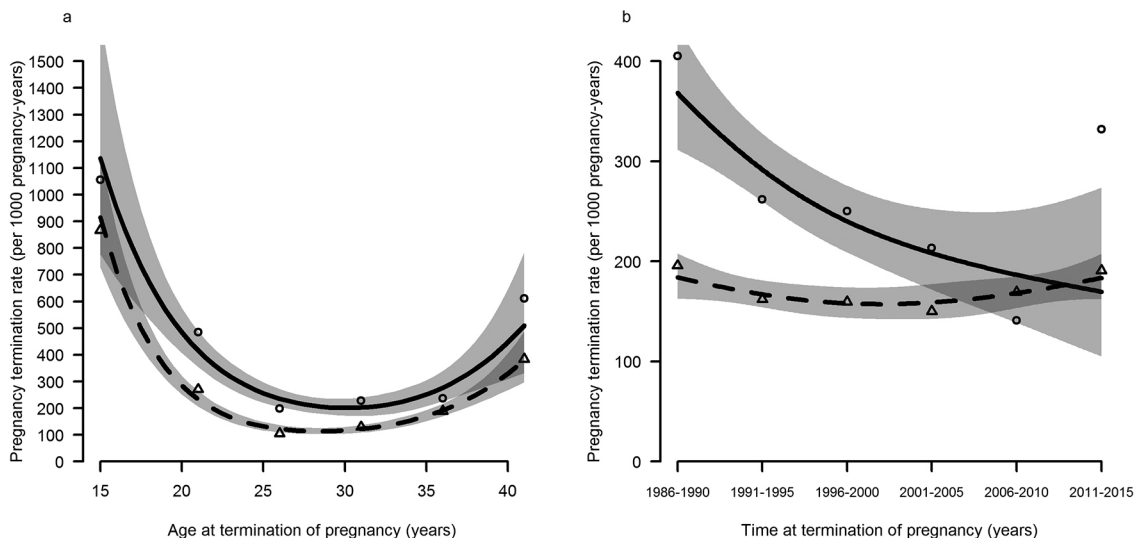


Figure 3. Rates of termination of pregnancy by age (A) and calendar time (B) among T1D women and control women. Solid line with circles, women with type 1 diabetes; dashed line with triangles, women without diabetes.

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When looking at the rate of terminations of pregnancy by age and by calendar time, it was observed that among women with T1D the number of terminations of pregnancy decreased before the year 2000 and then increased again – a phenomenon that was not seen among the women without diabetes.

Among the women without diabetes, the proportions of different indications for termination of pregnancy did not differ from the proportions in the general population. The proportions of indications in both groups are shown in Figure 4. The termination indications among the women with T1D differed from the indications among the control women: while maternal medical indications were almost absent (0.3%) among the control women, they were the reasons for 23.6% of terminations of pregnancy in the T1D group.

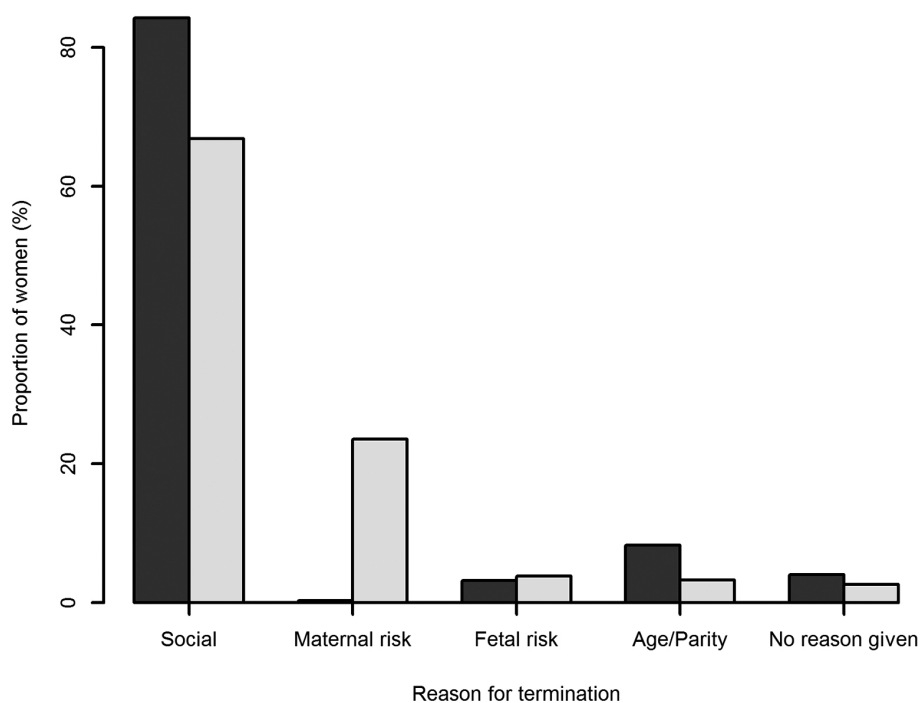


Figure 4. Proportions of indications for termination of pregnancy in women with and without T1D. Grey bars, women with type 1 diabetes; black bars, women without diabetes.

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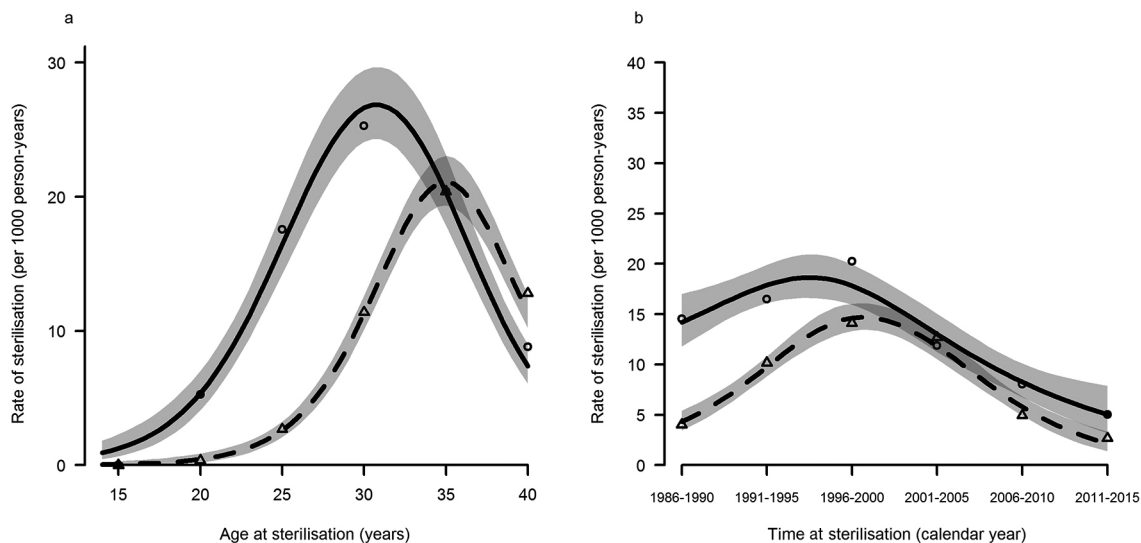


Figure 5: Sterilisation rates by age (A) and calendar time (B) among T1D women and control women. Solid line with circles, women with type 1 diabetes; dashed line with triangles, women without diabetes.

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The other main focus in Study II was sterilisation. There were significantly more sterilisation procedures among the women with T1D than among control women; the standardized incidence ratio was 1.69 (95% CI 1.56, 1.83). As in terminations of pregnancy, the indication spectrum among T1D women was very different from that in the control group: maternal medical indications were the reasons for 22.9% of the sterilisations in the T1D group, but only 0.3% of the sterilisation indications among control women.

The difference in sterilisation rates between the groups vanished around the year 2000. At about the same time, the sterilisation rates started to decline in both groups.

Almost all (26 of 27) of the sterilisations performed among childless women under the age of 30 concerned women with diabetes. Of all sterilisations performed among women under 30 years of age, 141 of 185 (76%) were carried out in women with diabetes and 44 of 185 (24%) in women without diabetes.

5.3 Menopausal age and factors associated with it

The respondents in Study III had a median age of 48.3 years. Their median age at onset of T1D was 12.9 years. The majority of them (86%) had children and 56% had more than one child. Neuropathy was reported by 28% and proliferative retinopathy by 47%. Nephropathy of some degree was reported by 26%; of these, 65 reported having progressed to end-stage renal disease.

Of the 640 eligible respondents with T1D (Figure 1), 87 women had undergone hysterectomy and four had chemical menopause as a result of chemotherapy. Hormonal contraception (causing amenorrhoea) was used by 30 women (most of them had a hormone-releasing intrauterine device). Forty-three women had started using hormone therapy for climacteric symptoms before the cessation of menses. The menopausal age of these 164 women could thus not be defined. These cumulative figures are based on both rounds of questionnaires.

Among the 640 respondents in Study III, there were 93 who had experienced natural menopause. The median age at menopause was 52.5 years. All factors listed in Table 6 were tested for association with age-related occurrence of menopause and the only factors that were associated with it were severe microvascular complications: women with end-stage renal disease or proliferative retinopathy reached menopause earlier than other women.

Table 6. Characteristics of the women in Study III.

Q_1 and Q_3 : the 25% percentile and the 75% percentile, respectively, of the distribution of the variable.

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Variable	Median	Q_1	Q_3
Age at diagnosis of type 1 diabetes (years)	12.9	10.7	15.2
Age at menarche (years)	13	12	15
Age at the time of the study (years)	48.3	45.9	51.0
		N	%
Parity	No children	92	14
	One child	189	30
	Two or more children	359	56
Smoking status	Non-smoker	309	48
	Ex-smoker	194	30
	Current smoker	133	21
Autoimmune diseases	Coeliac disease	38	5.9
	Hypothyroidism	171	27
	Rheumatoid arthritis	61	9.5
BMI (kg/m ²)	< 25	361	56
	25–30	203	32
	> 30	72	11
Hypertension (missing data: 0.5%)		254	40
Coronary disease (missing data: 1.1%)		50	7.8
Neuropathy (missing data: 0.1%)		177	28
Intermittent claudication (missing data: 12%)		53	8.3
Nephropathy (missing data: 0.3%)	no nephropathy	473	74
	proteinuria	95	15
	renal insufficiency	31	5
	end-stage renal disease (dialysis or renal transplantation)	39	6
Retinopathy (missing data: 6%)	mild retinopathy	321	53
	proliferative retinopathy	285	47

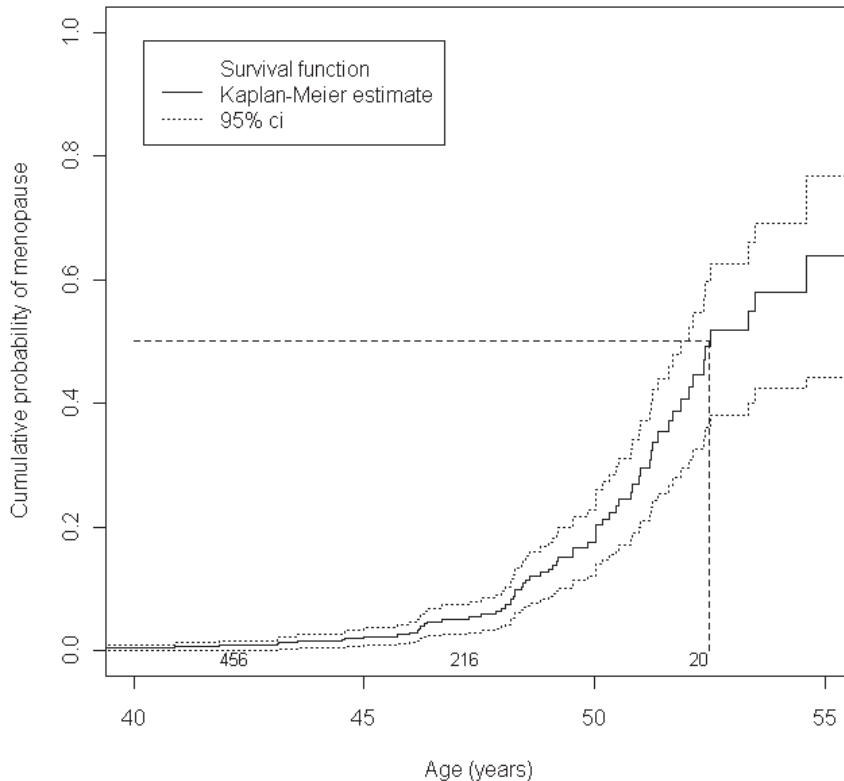


Figure 6. The cumulative probability of menopause as a function of age, together with the estimated median age (dotted line).

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Because of access to register data on all women in the cohort it was possible to compare the non-respondents with the respondents: those who participated in the questionnaire survey were more likely to have had children ($p < 0.001$) and to have had a higher age at diagnosis ($p < 0.001$).

5.4 Parity and mortality

In Study IV, the total mortality rate was much higher in women with T1D (5.3 per person-millennia) than in women without it (0.9 per person-millennia) ($p < 2 \times 10^{-16}$). All-cause mortality in women without children was significantly higher than in women with children, both among women with diabetes and without it ($p < 0.01$). Having at least one offspring was also associated with a decreased risk of diabetes-related death among women with diabetes (HR = 0.46; 95% CI 0.31, 0.69). There was a difference between the sexes: in men with offspring, the

decrease in mortality rate compared with men without offspring was less marked among those with diabetes (9% reduction in mortality hazard ratio (HR) with one offspring, 47% with two) than among those without diabetes (33% HR ($p = 0.025$) and 61% HR ($p = 0.023$) reduction, respectively). The corresponding decrease in mortality rate between women with and without offspring was independent of diabetes status among women. Furthermore, in men, having only one child was not associated with a decreased risk of dying from diabetes, but having two children was (Figure 7).

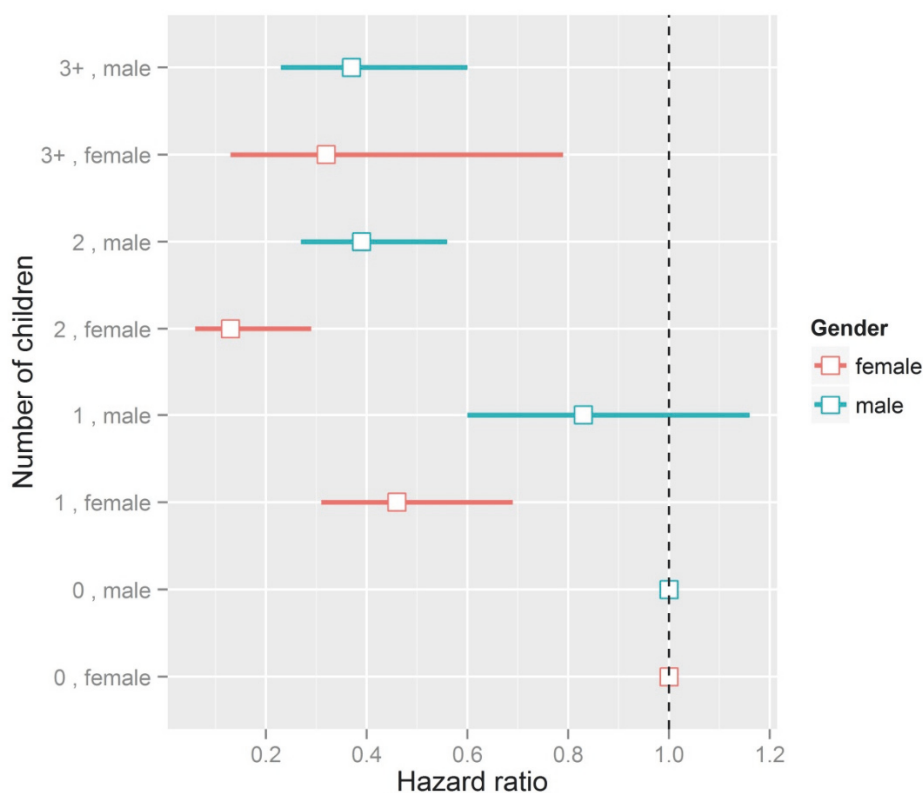


Figure 7. Diabetes-related mortality ratios (with 95% CI) in men and women by the number of live-born children.

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Looking separately at different causes of death, there were too few deaths from cardiovascular diseases among women without diabetes to allow comparison. In deaths from accidents and violence, and suicide, no statistically significant difference according to parity was seen in women without diabetes, but in women with diabetes, those with two children had a significantly reduced risk of dying from these causes.

6 DISCUSSION

The aim of this study was to investigate the reproductive health of women with childhood-onset type 1 diabetes from a population-based epidemiological perspective.

6.1 Main findings

Women with childhood-onset T1D have fewer children than women without T1D. Women in more recent birth cohorts tend to have more children than those in older cohorts. The later the age at onset of diabetes, the higher the probability of a woman with diabetes to have a second child.

Women with childhood-onset T1D have more terminations of pregnancy in relation to the number of birth events, and a greater sterilisation rate than women without diabetes. The spectrum of indications for both termination and sterilisation is very different in women with and without diabetes, with maternal medical indications in diabetic women being the reason for more than one fifth of cases of both termination and sterilisation, whereas such indications are virtually absent in women without diabetes.

Menopausal age in women with childhood-onset T1D does not seem to differ from that in the general population. In individuals with severe retinopathy or nephropathy, menopausal age is earlier than in women without microangiopathy.

The mortality rate among women with T1D is higher than in women without diabetes. Women with children have a lower mortality rate than childless women, regardless of diabetes status, but the difference in mortality rates according to parity is not as marked among men. Among women, having one child is associated with a significantly decreased risk of diabetes-related death, and having two children is associated with an even lower risk of diabetes-related death.

6.2 Interpretation of the findings

6.2.1 Fertility

Women with childhood-onset T1D have fewer children than women without diabetes and the differences between the groups diminish in later birth cohorts. No data is available on how many women with diabetes have made a choice on their own (or together with their partner) not to have children, how many have been influenced by healthcare professionals to make this decision – or how many have tried to get pregnant without succeeding.

Most studies carried out to explore parity in women with diabetes have not concerned voluntary versus involuntary infertility (20,39,41,89). A Danish study from 1992 was carried out to explore attitudes toward having children among women with T1D. More than half of them (111/197) reported that their diabetes had an influence on their attitude.

There are only a few studies on involuntary infertility in women with T1D. In a recent Norwegian study, pregnant women were asked about their time-to-pregnancy, i.e. the time taken before becoming pregnant. The participants with T1D ($n = 221$) reported a longer time-to-pregnancy than other women; the difference was statistically significant (41). An American study concerned 501 couples who planned pregnancy for twelve months. In couples with a female counterpart with T1D, there was a non-significant trend towards longer time-to-pregnancy than in couples without diabetes, and if the woman also had other medical conditions in addition to diabetes, e.g. hypothyroidism, the difference reached statistical significance (42). Of the respondents in our study (Study III), 27% reported hypothyroidism, which potentially makes this a clinically significant factor as regards reduced fecundity.

In Study III, the participants were asked whether they had undergone treatment for infertility. A total of 611 respondents of 640 (96%) replied to the question and 26 of them (4%) responded positively. This previously unpublished data indicates that involuntary infertility is not a more significant problem in this group of women than in the general population, which is in line with the results of some previous studies (19,90).

There might be many women (couples) who decide not to use contraception, but also not to consult a doctor if they fail to become pregnant – which makes differentiation of reasons for childlessness complicated (91). In a Scottish questionnaire study, four of 56 married women (7%) who had not wanted to have children stated that the reason for their childlessness was a chronic disease, but they did not report what disease (92). Studies on the extent to which a chronic disease affects the probability of seeking medical help in cases of fertility problems are scarce. In a general-practitioner-record-based British study the proportion of women who were childless by choice was increased in younger cohorts, but the authors reported no data on diseases among the participants (93). The researchers

were very cautious in asking questions of their study patients and pointed out that the matter is very sensitive and that probing into it might produce both distress and incorrect replies. Other researchers (39) have also reported having made a decision not to ask about individual reasons for childlessness.

Future studies could be aimed at exploring the characteristics of women with T1D who do not have any children. Register data on co-morbidity could provide some new information. Studying patient data on metabolic control would be even more valuable in differentiating between women with different reproductive patterns (no pregnancies – only abortions – one or more deliveries).

6.2.2 Terminations of pregnancy and sterilisation

In 1987–2011, the time interval in the study involving terminations of pregnancy and sterilisation (Study II), 0.6% of all sterilisation procedures performed among Finnish women had a maternal medical indication (53). This is of the same magnitude as in our study, where 0.3% of both terminations of pregnancy and sterilization procedures in control women were undertaken for maternal medical reasons. This indicates that our control group reflects the general population of Finland.

In this study, medical reasons were behind 23.6% of terminations of pregnancy and 22.9% of sterilisation procedures in women with diabetes. It is probable that many of these maternal medical reasons in the cases of termination of pregnancy reflect poor metabolic control in early pregnancy, but this could not be verified since the only patient records available were the application forms. If this is the case, it reflects the fact that not all women with T1D carefully plan their pregnancies, or at least they do not succeed in achieving optimal metabolic control before conception. Pregnancy planning in women with T1D has increased during the last few decades; in a recent Finnish study, 66.2% of pregnancies in women with T1D were planned (94).

In cases of sterilisation, some of the procedures undertaken on the basis of maternal medical indications probably are strongly recommended by physicians, and some of them are performed according to the wishes of the patient and it is difficult to speculate on the proportions of these two. Studying patient records would provide more insight into the individual situations of women with T1D who undergo terminations of pregnancy.

Looking into possible regional differences could also provide new insight: Do regional differences in diabetes treatment influence metabolic control and, subsequently, also the frequency of terminations of pregnancy? A comparison between countries based on these differences is another perspective in future studies.

The number of terminations of pregnancy in women with T1D fluctuated: they decreased before the year 2000 and then increased again. This cannot be explained by any changes in legislation or guidelines. The phenomenon was not seen in women without diabetes. It is probably related to the age distribution in the cohort; during the late 1980s and 1990s, a large proportion of women in the cohort were in their thirties and had their children at that age. The women with diabetes in our cohort seldom had children after the age of 40, whereas the women without diabetes had their children more evenly throughout their fertile time period. Women with diabetes could have acquired diabetic complications after a relatively long disease duration and therefore not wanted to risk their health by having another child, which could explain part of this trend. In our cohort, it is difficult to estimate the extent to which the general progress in preventing diabetes complications has influenced pregnancy planning and pregnancy outcomes in different birth cohorts, because there are relatively few women born in the 1970s.

The reasons for the decline in sterilisation procedures in both groups of Finnish women after the year 2000 are not clear. One reason may be that sterilisation of men has increased steadily (14). The use of hormonal intrauterine devices has also increased and they are seen as a safe alternative for birth control. There are no statistics or recent Finnish studies on the use of different contraceptive methods among women with T1D.

6.2.3 Menopausal age and factors associated with it

Our results indicate that T1D does not lead to earlier than average menopause, if no severe microvascular complications are present. This is in contrast with the results of two previous studies from the US, where menopause occurred 6–8 years earlier in women with T1D than in women without diabetes (24,62). There are more recent studies that support our results, both from Europe and from the US (63,64), but these studies did not include information about complications. The results from the DERI mortality study indicated that persons with childhood-onset T1D in the USA had a higher mortality rate and a higher rate of complications than Finnish persons with T1D (80), which might partly explain the differences between the countries regarding menopause issues in women with T1D.

This is another link in the chain of study results suggesting “normalization” of the lives of women with T1D. On the other hand, if proliferative retinopathy and end-stage renal disease are associated with earlier menopause, there is a definite clustering of risk factors in those women with T1D who have microangiopathy.

Interestingly, in our study no association was seen between the age-related prevalence of menopause and many of the factors traditionally considered to be associated with menopause: BMI, smoking, parity and education level. The relatively small sample might explain the fact that none of these associations

were seen. None of the autoimmune diseases included in the study (coeliac disease, hypothyroidism and rheumatoid arthritis) were associated with the age-related prevalence of menopause; neither was macroangiopathy (coronary heart disease, peripheral arterial disease). The most severe forms of both retinopathy and diabetic nephropathy were the only factors associated with the age-related prevalence of menopause. This supports the theory that early menopause could have a vascular aetiology: the presence of severe microangiopathy often suggests poor long-term metabolic control, resulting in arterial changes in various organs, including the ovaries – and, on the other hand, an earlier menopause could alter the cardiovascular risk profile in an unfavourable direction.

Menopause research is impeded by the fact that cessation of menstruation does not always mean natural menopause. When studying the menopause and especially menopausal age, there are several factors that influence interpretation of the results. Lack of menstrual bleeding may be the result of reasons other than natural menopause. Hysterectomy/oophorectomy naturally leads to surgical menopause. Chemical menopause occurs when menstrual bleeding stops because of the use of chemotherapy.

The most common of other reasons for cessation of menstruation is the use of hormonal contraceptive methods, mainly hormonal intrauterine devices. If a woman starts using hormonal therapy to alleviate climacteric symptoms before the natural cessation of menses, age at the time of natural menopause cannot be defined. Among women with severe renal disease, menstrual bleeding may cease without the woman having entered menopause (95). All these factors reduced the number of women who could in this study be dichotomized as premenopausal or menopausal.

6.2.4 Parity and mortality

Type 1 diabetes still affects life expectancy, although much improvement has occurred since the 1920s, when insulin treatment started (96). The association between a higher mortality rate and being childless is very complex and needs to be assessed by using methodology other than a medical research paradigm; to compare this association in women with a chronic childhood-onset disease such as T1D and other women also demands a broader perspective than a purely medical one. Before drawing the conclusion that low parity leads to a higher mortality rate, one must exclude the opposite: that a high risk of mortality results in low parity.

There are sex differences in our results regarding the association between parity and mortality in persons with and without diabetes. When looking at diabetes-related death, having at least one offspring was associated with a decreased risk of diabetes-related death among women (HR=0.46; 95% CI 0.31, 0.69); in men, no difference was seen among those with only one offspring, but in men with two

offspring, there was a significant decrease in diabetes-related mortality compared with men without offspring. As regards overall mortality, the decrease in mortality in persons with offspring compared with those without offspring was much less marked among men with diabetes than in any other group (Figure 7).

A woman with diabetes commonly undergoes very meticulous control during pregnancy in order to ensure normal development of the foetus. Some studies have indicated that good motivation, and the information provided to women in specialist clinics during pregnancy, support women in maintaining good metabolic control after delivery (31,97). Naturally, this does not apply to men. This difference might explain some of the differences in parity-related mortality between the sexes.

6.3 Methodological considerations

6.3.1 Data sources

The cohort that has been studied was established in the 1980s, utilizing the registers of The Social Insurance Institution of Finland. Persons who had applied for reimbursement of costs arising from insulin treatment of T1D and who were under 18 years of age on the day of diagnosis were included in the cohort. Since there are virtually none who do not apply for reimbursement of costs, and because much effort was made to verify each case, the cohort has been considered complete. The diagnostic criteria applied when the cohort was established are still valid, although much more is known nowadays about other forms of diabetes, and more diagnostic tests are available. Records of each person potentially suitable to be included in the cohort were individually evaluated for the type of diabetes, date of diagnosis and age at onset (84).

When selecting the control persons, they were matched according to sex and geographical region. These parameters are relevant, because the incidence of T1D is different in males and females and this has also made the study of reproductive questions easier. Matching according to geographical region diminishes the effect of any confounding factors related to this aspect. The fact that the frequency of terminations of pregnancy among our control women was equal to the corresponding figure in the general population indicates that selection of the controls has succeeded.

6.3.2 Questionnaire study

The response rate in the menopause study was 66% in the first round and 83% in the second round. Not all potential participants could be contacted, either because of lack of a valid address or because it was not possible to get permission

to contact them, since there was no data on any recent health service contacts. Tens of women in the cohort had already died when this study started, many of them before reaching menopause, resulting in bias if factors related to the causes of death are also connected to the age-related occurrence of menopause. Since register data was available on all potential participants, it was possible to compare respondents with non-participants as regards baseline information. The respondents had more children and had been diagnosed with diabetes later in life than the non-participants (both differences statistically highly significant). How these differences would have affected the results regarding menopausal age is difficult to explore. If there were to be a strong association between age at onset of diabetes or parity on the one hand and the age-related occurrence of menopause on the other hand, there could be a significant bias.

One potential source of bias in this study is the fact that a major proportion of the data is self-reported, including data on retinopathy and nephropathy, where information can be misunderstood when passed from doctor to patient.

6.4 Strengths and limitations of the study

Because of the large cohort of cases of childhood-onset T1D and good availability of external data from other national registers, with virtually complete coverage, it was potentially possible to find even small differences in the parameters studied. The population controls utilized in three of the four studies can be considered to be representative, given birth year and location.

The national reimbursement policy diminishes bias due to regional variation, and national personal identification codes enable high-quality data linkage.

Since the rate of childhood mortality in Finland is very low (98), causes of death are investigated in all cases and all indefinite cases are carefully considered. Hence, no diabetes cases are thought to have been missed at the time of establishment of the cohort. The only exception could be in 1965–1969, when causes of death could not be completely ascertained, although it has been estimated that it is very improbable that many cases, if any at all, have been missed (84).

In Finland, mortality follow-up is virtually complete as a result of reliable register data (99,100) and the fact that a unique identifier, a national identification number, is used in linkage processes. In only a few cases was there somewhat unclear classification of the immediate cause of death.

When fertility was explored, the sources were both The Hospital Discharge Register of the National Institute of Health and Welfare (ICD diagnoses of delivery), and linkage of mothers and offspring was through The Population Register. Since almost no children are born outside public hospitals in Finland, the Hospital Discharge Register might well have sufficed for assuring that no births are missing.

Terminations of pregnancy have been approved by Finnish law since 1950, termination for social reasons was legalised in 1971 and illegal terminations of pregnancy are considered to have stopped at the start of the 1970s, at the latest. Our main data source here was The Register on Induced Abortions. The reliability of Finnish registers has been evaluated over the years and they are generally considered to be very reliable (7–10,101).

The data source for Study III was a questionnaire. Questionnaires always contain self-reported participant data and the participant can choose not to tell certain things, or even give false information.

Regarding menopausal age, which is always self-reported, it has been observed that the probability of correct recall has been higher when less time has passed since menopause (102). Most of the women who had reached menopause had done so within five years prior to the survey. There was very little inconsistency in the reported ages at menopause in women who reported their menopausal age in both surveys, sent three years apart. In cases of inconsistency, the reported age in the first survey was used, because it was nearer the actual date of menopause.

The main limitations of Study III are related to the general weaknesses of survey studies and to the particular weakness of our questionnaire study implementation. The participation rate could have been higher had the forms been made more anonymous, e.g. by removing the participant's printed name from the form and substituting it with a number code. Although the forms were sent in closed envelopes (and discreet return envelopes), the name on the form might have mattered to some of the potential respondents. The nature of the data gathered via this questionnaire was fairly intimate, which probably reduced the number of respondents.

The present work is connected to childbirth without directly dealing with the offspring of the women participating in the study. It is very evident that the reproductive health of women also involves the well-being of the next generation. The health of the offspring affects decisions regarding family planning and is therefore in focus in most studies regarding reproductive health matters among women with T1D. There are far more previous studies on pregnancy outcome in T1D than on the issues covered by our study: family size, terminations of pregnancy, sterilisation, menopause and parity-related mortality.

A general problem in research involving parity issues is the varying terminology: the term fertility is frequently used imprecisely. In some studies, fertility is explored, but when drawing conclusions, the results are interpreted as though they could also provide data on fecundity. Exploring quantitative data on family sizes and numbers of live births does not include any information on the intentions and desires of women who have given birth and those who have not.

7 CONCLUSIONS AND IMPLICATIONS FOR FURTHER STUDIES

For women with childhood-onset T1D, the results of our study provide positive information. When looking at time trends in fertility, sterilisation and age at menopause, the differences between women with and without diabetes as regards many reproductive health issues have decreased with time. This is probably partly due to progress in the treatment of diabetes. Good metabolic control and improved treatment possibilities combined with increased knowledge in the field of reproductive health in T1D encourages women to become pregnant without fear of complications due to T1D.

To go beyond the current register-based studies would deepen our knowledge of reproductive health issues in women with T1D. In a prospective setting, metabolic control, risk factors, diseases other than diabetes and factors other than health-related aspects that influence both reproductive health and mortality could be identified. Qualitative studies could provide data on the reasons behind low parity, e.g. in connection with voluntary versus involuntary infertility. Surveys and in-depth interviews could also give a more nuanced picture of how health professionals have influenced the decisions made by women and by couples.

The sterilisation rate in women with diabetes has reached the rate observed in the general population. This reflects the fact that no currently used contraceptive methods are contraindicated in women with diabetes – and may also reflect the fact that pregnancy seldom is considered totally contraindicated because of diabetes.

If menopausal age is not earlier in women with T1D, the reproductive life span is not shorter than in other women. This might decrease worry about whether one is in a hurry to have children because of diabetes – if neither macroangiopathy nor severe microangiopathy is present.

No definite indications have been found that there are factors that influence the association between parity and mortality other than the tendency to decide not to have (more) children if there are diabetic complications or other factors that affect the prognosis, which means that the results of this study are concordant with those of previous studies.

The treatment of T1D has steadily developed in recent decades and studying the reproductive health of younger cohorts is important in the future. Those who are born in the 21st century and are diagnosed with T1D receive all the benefits from the latest diabetes research and therefore have a different risk profile than the women in our cohort, who were diagnosed in the 1960s and 1970s. The intrinsic factors influencing the patients' motivation to maintain good metabolic control are, however, not much different from those in previous generations.

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At first, the project was to be only about menopause in women with diabetes. Soon it became clear that this topic was too narrow. By that time I had learned to know Laura Haapala, who was working on her master's thesis on the family size of people with childhood-onset type 1 diabetes, and Janne Pitkaniemi, who worked in the same room as Laura. The idea of widening my topic to include all aspects of reproductive health of women with type 1 diabetes led to cooperation with both Laura and Janne. Janne became my third supervisor in 2012. Janne: thank you for all the moments we have shared together, often laughing till we cried while working. You have become my friend and the only negative thing about finishing my thesis is that we might not work together anymore.

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Lena Sjöberg

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Appendix

Questionnaire of Study III in Finnish

Kansanterveyslaitos / HUS Naistenklinikka

NAISDIABEETIKON TERVEYSTUTKIMUS

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Yleistiedot:

Osoite: _____
(mikäli muuttunut)

Puh: _____

Sähköposti: _____

Diabetestiedot:

Toteamisvuosi: 19 _____

1. Onko suvussanne muilla diabetesta (nuoruusiän eli tyypin 1 diabetesta)?

1 kyllä ---->

kenellä: _____

2 ei

3 en tiedä

2. Missä Teitä hoidetaan diabeteksenne vuoksi?

3. Viimeisin HbA1c-arvo ("pitkäaikaissokeri"): _____

3.1 Missä viimeisen vuoden HbA1c-arvot on mitattu:

Päivämäärät (jos muistatte): _____

4. Onko silmämuutoksia?

- 1 Kyllä ----- > Milloin todettu ensimmäisen kerran? _____
- 2 Ei
- 3 En tiedä

4.1 Minkä asteisia muutoksia?

- 1 Taustaretinopatiaa
- 2 Proliferatiivista retinopatiaa
- 3 Ei muutoksia
- 4 En tiedä

4.2. Onko laserhoitoa annettu?

- 1 Kyllä ----- > kuinka monta kertaa: _____
- 2 Ei

5. Missä ja milloin viimeisin silmätutkimus? _____

6. Onko munuaismuutoksia?

- 1 Kyllä ----- > milloin todettu? _____
- 2 Ei

6.1 Minkä asteisia muutoksia ?

- 1 Valkuaista virtsassa
- 2 Munuaisten vajaatoimintaa

6.2. Onko munuaisten vajaatoiminta vaatinut dialyysin tai munuaistensiirron?

- 1 Kyllä
- 2 Ei

7. Onko teillä todettu kohonnut verenpaine (> 140/90 mmHg)?

- 1 Kyllä
- 2 Ei

7.1 Käyttätkö verensokerilääkettä?

1 Kyllä -----> minkä

nimistä? _____

2 En

8. Onko teillä todettu ääreishermoston muutoksia (neuropatiaa)?

1 Kyllä

2 Ei

9. Onko teillä todettu sepelvaltimotautia?

1 Kyllä -----> Miten hoidettu: lääkehoito ☐ pallolaajennus ☐ ohitusleikkaus ☐

2 Ei

10. Onko teillä todettu ääreisverenkierron häiriöitä (esim. katkokävelyä)?

1 Kyllä

2 Ei

B) Muut sairaudet:

Onko teillä todettu - ja jos on, miten hoidettu/hoidetaan

1. Kilpirauhassairaus

1 Kyllä -----> hoito: _____

2 Ei

2. Reumatauti (nivelreuma, Sjögrenin oireyhtymä, LED)

1 Kyllä -----> hoito: _____

2 Ei

3. Astma

1 Kyllä

2 Ei

4. Syöpä

1 Kyllä ----- > minkä elimen syöpä? _____

hoito: _____

2 Ei

5. Keliakia

1 Kyllä

2 Ei

6. Muita kroonisia sairauksia

1 Kyllä ----- > mitä? _____

hoito: _____

2 Ei

7. Luukato (osteoporoosi)

1 Kyllä

2 Ei

jos on esiintynyt murtumia, niin kirjatkaa tähän minkälaisia

D) Gynecologiset esitiedot:

1. Kuukautisten alkamisikä: _____
2. Kuukautiskierron pituus: _____
(kuinka monta päivää kuukautisten alkamisesta seuraavien kuukautisten alkamiseen)
3. Kuinka monta päivää kuukautisvuoto kestää (tai kesti, mikäli ne ovat loppuneet)?
_____pv
4. Onko(oliko) teillä välivuotoja?
 - 1 Kyllä
 - 2 Ei
5. Onko teillä ollut poikkeuksellisen paljon akneongelmia (finnejä)?
 - 1 Kyllä
 - 2 Ei
6. Kärsittekö mielestänne liiallisesta ihokarvoituksesta?
 - 1 Kyllä
 - 2 En
7. Käytättekö nyt ehkäisypillereitä?
 1. Kyllä; merkki: _____
 2. En
8. Käytättekö nyt kierukkaa?
 1. Kyllä ☐ kuparikierukkaa ☐ hormonikierukkaa
 2. En

9. Onko lääkäri määrännyt lisälääkitystä epäsäännöllisten tai poisjääneiden kuukautisten takia?
1. Kyllä ——— mitä valmistetta ja milloin? _____
 2. Ei
10. Kuinka monta raskautta teillä on ollut?
- Synnytyksiä: _____
- Keskenmenoja: _____
- Raskaudenkeskeytyksiä (abortteja): _____
- Kohdunulkoisia raskauksia: _____
11. Onko raskauksien yhteydessä ollut verenpaineen nousua ja/tai valkuaista virtsassa ("raskausmyrkytys")?
1. Kyllä ----- > minä vuonna/vuosina? _____
 2. Ei
12. Ikänne synnytysten yhteydessä: _____
13. Oletteko saanut lapsettomuushoitoa?
1. Kyllä ----- > minkälaista ja milloin? _____
 2. En
14. Onko teillä ollut gynekologisia sairauksia (esimerkiksi tulehduksia, endometrioosi)?
1. Kyllä ----- > minkälaisia sairauksia? _____
Miten teitä on hoidettu? _____
 2. Ei
15. Onko teille suoritettu kohdunpoistoleikkaus?
1. Kyllä ----- > minä vuonna? _____
 2. Ei
16. Onko teille suoritettu munasarjojen poistoleikkaus?
- 1 Kyllä ----- > minä vuonna? _____
 - 2 Ei
 - 3 Vain toinen munasarja poistettu

E) Vaihdevuositiedot

1. Minkä ikäisenä äitinne koki vaihdevuodet? _____

1. En tiedä

2. Onko äitinne vielä elossa?

1. Kyllä

2. Ei

3. Minkä ikäisenä mahdolliset sisarennne kokivat vaihdevuodet? _____

1. Ei ole sisaria-----→ siirtykää kysymykseen 6

2. Sisarillani ei ole vielä vaihdevuosi

3. En tiedä

4. Montako elossa olevaa siskoa teillä on? _____ siskoa

_____ sisarpuolta

Siskojenne syntymävuodet: _____

Sisarpuolten syntymävuodet: _____

5. Sairastaako joku siskoistanne diabetesta?

1. Kyllä, vuonna _____ syntynyt/syntyneet

2. Ei

6. Onko teillä vielä kuukautiset?

1. Kyllä

2. Ei

7. Ovatko kuukautisenne harventuneet tai jääneet välillä pois?

1. Kyllä

2. Ei

8. Milloin teillä oli viimeiset kuukautiset? _____

9. Onko teillä viimeksi kuluneen kuukauden aikana ollut seuraavanlaisia oireita (jotka saattavat olla merkki vaihdevuosista)? Ilmoittakaa jokaisessa kohdassa oireiden voimakkuus (0= ei oireita, 5= sietämättömät):
1. kuumia aaltoja
 2. hikoilua
 3. unettomuutta
 4. ärtyisyyttä
 5. sydämentykytystä
10. Käytättekö tällä hetkellä hormonihoitoa?
1. Kyllä -----> valmisteiden nimi: _____ milloin aloitettu: _____
 2. En-----> Oletteko saanut vaihdevuosioireisiin hormonihoitoa aikaisemmin?
 1. Kyllä; minä vuosina? _____
 2. En koskaan
9. Jos olette saanut hormonihoitoa, onko se auttanut mahdollisiin oireisiinne?
1. Kyllä
 2. Ei
 3. Ei ollut oireita
 4. En ole saanut hormonihoitoa-----> ohittakaa kysymykset 10 ja 11
10. Onko vaihdevuosien hormonihoito aiheuttanut sivuvaikutuksia?
1. Kyllä ----- > minkälaisia? _____
 2. Ei
11. Vaikuttiko vaihdevuosien hormonikorvaushoito diabetestasapainoonne?
1. Kyllä ----- > miten? _____
 2. Ei

F) Depressio

1. Oletteko joskus hakeutunut lääkärin/psykologin/muun ammatti-ihmisen puheille alakuloisuuden tai masentuneisuuden takia?

1. Kyllä-----→ milloin? _____

2. En

2. Onko teille milloinkaan määrätty lääkitystä masennuksen eli depression hoitoon?

1. Kyllä-----→ vuosina _____

Muistatteko mitä lääkettä? _____

2. Ei

3. Tunnetteko tällä hetkellä itsenne masentuneeksi?

1. Kyllä

2. En

3. Olkaa hyvä ja täyttäkää oheinen lomake (DEPS-masennusseulonta).

G) Elintavat yms

Paino: _____ Pituus: _____

1. **Kolesteroliarvonne**

Milloin viimeksi mitattu: _____

1.1 Kokonaiskolesteroli: _____

1.2 HDL-kolesteroli (ns hyvä kolesteroli): _____ triglyseridit: _____

2. **Harrastatteko liikuntaa? eli kävelettekö/pyöräilettekö/uitteko/hiihdättekö yli puoli tuntia kerrallaan ja vähintään 3 kertaa viikossa?**

1. Kyllä

3. En

3. Oletteko koskaan tupakoinut?

1. Kyllä
2. En-----→ siirtykää kysymykseen 4

3.1. Milloin aloititte tupakanpolton? Vuonna _____

Tupakoitteko nyt?

1. Kyllä -----> montako savuketta päivässä? _____
2. En

3.2. Jos olette lopettanut: milloin lopetitte?_____
kuinka monta vuotta tupakoitte kaikkiaan? _____

4. Käytättekö alkoholia (2 annosta tai enemmän, 1 annos= pullo olutta tai lasi viiniä tai 4 cl väkeviä)

1. päivittäin
2. viikoittain
3. 1-2 kertaa kuukaudessa
4. harvemmin
5. en lainkaan

5. Mikä on peruskoulutustasonne? (merkitkää pisin koulutus, vain yksi vaihtoehto)

1. Kansakoulu, keskikoulu tai peruskoulu
2. Ammattikoulu/keskiasteen tutkinto (myös nykyinen ammattikorkeakoulu)
3. Ylioppilastutkinto
4. Korkeakoulututkinto

paikka

pvm

allekirjoitus

nimen selvennys

KIITOKSIA VAIVANÄÖSTÄNNE !

Folkhälsoinstitutet / HNS, Kvinnokliniken

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HÄLSOUNDERSÖKNING FÖR KVINNLIGA DIABETIKER

Kontaktuppgifter:

Adress: _____
(ifall den ändrats)

Telefon: _____

E-post: _____

Diabetesuppgifter:

1. Har någon av Era släktingar diabetes (ungdomsdiabetes, dvs typ 1 diabetes)?

1 ja ----> vem/vilka (släktskapsförhållande): _____

2 nej

3 vet inte

2. Var uppföljs Ni pga. Er diabetes (vilken privatläkare, hälsocentral eller sjukhuspoliklinik)?

3. Senaste HbA1c-värde ("långtidssocker"): _____

3.2 Var har det senast gångna årets HbA1c-värden uppmätts:

Hur många gånger per år brukar HbA1c mätas? _____

4. Har ögonbottenförändringar konstaterats?

- 1 Ja ----- > När konstaterades de första gången? _____
- 2 Nej
- 3 Vet inte

Vilken grad av ögonbottenförändringar?

- 1. Bakgrundsretinopati
- 2. Proliferativ retinopati
- 3. Inga förändringar
- 4. Vet inte

4.2. Har Ni fått laserbehandling?

- 1 Ja ----- > hur många gånger: _____
- 2 Nej

5. När och var undersöktes ögonbottenarna senast?

6. Har njurfunktionen försämrats på grund av diabetes?

- 1 Ja----- > När har detta konstaterats? _____
- 2 Nej

6.1 Vilken grad av förändringar?

- 1 Protein (äggvita) i urinen
- 2 Njursvikt

6.2. Har njursvikten lett till dialysbehandling eller njurtransplantation?

- 1 Ja
- 2 Nej

7. Har Ni förhöjt blodtryck(> 140/90 mmHg)?

- 1 Ja
- 2 Nej

7.1 Använder Ni blodtrycksmediciner?

- 1 Ja ----- > vilken medicin? _____
- 2 Nej

8. Har Ni konstaterats ha förändringar i nervfunktionerna (neuropati – t.ex. känseln nedsatt i fötterna)?

- 1 Ja
- 2 Nej

9. Har Ni kranskärslssjukdom (hjärtsjukdom med syrebrist i hjärtat)?

- 1 Ja ----- > Vilken behandling: mediciner ☐ ballongutvidgning ☐ by-pass-operation ☐
- 2 Nej

10. Har Ni försämrad blodcirkulation i benen (t.ex. klaudikation = ”fönstertittarsjuka”)?

- 1 Ja
- 2 Nej

B) Andra sjukdomar:

Har Ni följande sjukdomar? - ifall ja, hur behandlas/behandlades de

1. Sköldkörtelsjukdomar

- 1 Ja ----- > behandling: _____
- 2 Nej

2. Reumatiska sjukdomar (ledgångsreumatism, Sjögrens syndrom, LED)

- 1 Ja ----- > behandling: _____
- 2 Nej

3. Astma

- 1 Ja
- 2 Nej

4. Cancer

- 1 Ja ----- > vilket slag av cancer? _____
Behandling: _____
- 2 Nej

5. Celiaki

- 1 Ja
- 2 Nej

6. Andra kroniska sjukdomar

- 1 Ja ----- > vilka? _____
behandling: _____
- 2 Nej

7. Benskörhet (osteoporos)

- 1 Ja
- 2 Nej

Om Ni har haft benbrott, var vänlig och skriv här hurudana

D) Gynekologiska uppgifter:

1. Hur gammal var Ni då Ni fick Er första menstruation? _____
2. Menstruationscykelns längd: _____
(hur många dagar från menstruationens början till följande menstruation)
3. Hur många dagar blöder Ni (eller blödde, ifall Ni inte längre har menstruation)?
_____ dagar
4. Har (hade) ni mellanblödningar?
 - 1 Ja
 - 2 Nej
7. Använder Ni p-piller för tillfället?
 1. Ja; märke: _____
 2. Nej
8. Har Ni spiral?
 1. Ja ☐ kopparspiral ☐ hormonspiral
 2. Nej
9. Har Ni fått hormonbehandling på grund av oregelbunden eller utebliven menstruation?
 1. Ja _____
vilket preparat och när? _____
 2. Nej
10. Hur många graviditeter har Ni haft?

Förlossningar: _____
Missfall: _____
Aborter: _____
Utomkvedshavandeskap: _____

11. Har Ni haft förhöjt blodtryck och/eller protein i urinen under graviditet ("graviditetsförgiftning")?
1. Ja ----- > vilket/vilka år? _____
 2. Nej
12. Hur gammal var Ni då Ni födde Era barn: _____
13. Har ni fått behandling för barnlöshet?
1. Ja ----- > hurudan behandling och när?

 2. Nej
14. Har Ni haft gynekologiska sjukdomar (t.ex. infektioner, endometrios)?
1. Ja ----- > hurudana sjukdomar? _____
Hurudan behandling har Ni fått för dessa? _____
 3. Nej
15. Har Er livmoder opererats bort?
1. Ja ----- > vilket år? _____
 2. Nej
16. Har äggstockarna opererats bort?
1. Ja ----- > vilket år? _____
 2. Nej
 3. Endast ena äggstocken bortopererad
17. Har Ni genomgått steriliseringsoperation?
- 1 Ja
 - 2 Nej

E) Uppgifter om övergångsåren

1. Hur gammal var Er mor då hon kom i klimakteriet (dvs. när slutade hennes menstruation)? _____
Vet inte _____
2. Lever Er mor?
 1. Ja
 2. Nej
3. Vid vilken ålder slutade Era eventuella systrars menstruation? _____
 1. Har inga systrar-----→ gå till fråga 6
 2. Mina systrar är ännu inte i klimakteriet
 3. Vet inte
4. Hur många systrar har Ni i livet? _____ systrar
_____ halvsystrar
Era systrars födelseår: _____
Era halvsystrars födelseår: _____
5. Har någon av Era systrar diabetes?
 1. Ja, den/de som är född/födda år _____
 2. Nej
6. Har Ni ännu kvar Er menstruation?
 1. Ja
 2. Nej
7. Har Er menstruation ibland uteblivit eller har den börjat komma mer sällan än förut?
 1. Ja
 2. Nej
8. När hade Ni Er senaste menstruation? _____

9. Har ni under den senast gångna månaden upplevt något av följande symptom (som kan vara ett tecken på klimakterium = övergångsåren)? Skriv in vid varje symptom hur starka symptom Ni haft på en skala från 0 till 5:

0=inga symptom, 1=mycket lindriga symptom, 2= lindriga symptom, 3= medelsvåra symptom, 4=svåra symptom. 5= olidligt starka symptom:

1. värmesvallningar ("heta vågor")
2. riklig svettning
3. sömnlöshet
4. lättretlighet
5. hjärtklappning

10. Använder Ni hormonbehandling (annan än p-piller) för tillfället?

1. Ja -----> medicinens namn: _____

När har behandlingen påbörjats? _____

2. Nej-----> Har Ni tidigare fått hormonbehandling **för klimakteriebesvär**?

1.Ja; när? _____

2. Nej

9. Om Ni fått hormonbehandling, har den hjälpt mot Era symptom?

1. Ja

2. Nej

3. Hade inga symptom

4. Har inte fått hormonbehandling-----> hoppa över frågorna 10 och 11

10. Har hormonbehandlingen gett biverkningar?

1. Ja ----- > hurudana? _____

2. Nej

11. Har hormonbehandlingen för klimakteriesymptom påverkat er sockerbalans?

1. Ja ----- > hur? _____

2. Nej

G) Depression

1. Har Ni någon gång sökt hjälp hos t.ex. läkare eller psykolog på grund av nedstämdhet eller depression?

1. Ja-----→ när? _____

2. Nej

2. Har Ni någon gång använt depressionsmediciner?

1. Ja-----→ under åren _____

Minns Ni medicinens namn? _____

2. Nej

3. Känner Ni Er deprimerad för tillfället?

1. Ja

2. Nej

3. **Var vänlig och füll i bifogade blankett (DEPS-depressionssållning).**

Vikt: _____ Längd: _____

1. **Era kolesterolvärden**

När har kolesterolet senast uppmätts? _____

Om Ni känner till de senast uppmätta värdena, var vänlig och skriv in dem nedan.

1.1 Total kolesterolhalt (S-kol): _____

1.2 HDL-kolesterol (s k godartat kolesterol): _____ triglycerider: _____

2. **Motionerar Ni? dvs promenerar/cyklar/simmar/skidar/gymnastiserar Ni minst en halv timme åt gången minst 3 gånger i veckan?**

1. Ja

2. Nej

3. Har Ni någonsin rökt?

1. Ja
2. Nej-----→ gå till fråga 4

3.1. När började Ni röka? År _____

Röker Ni nuförtiden?

1. Ja -----> hur många cigaretter per dag? _____
2. Nej

3.2 Om Ni slutat: när slutade Ni röka? _____

Hur många år rökte Ni allt som allt? _____

4. Använder Ni alkohol (2 portioner eller mer; 1 portion= en flaska öl eller ett glas vin eller 4 cl starksprit)

1. dagligen
2. varje vecka
3. 1-2 gånger per månad
4. mer sällan
6. inte alls

5. Vilken är Er grundutbildning? (endast ett alternativ)

5. Folkskola, mellanskola eller grundskola
6. Yrkesskola/mellanstadieutbildning
7. Studentexamen
8. Universitets- eller högskoleexamen

ort

datum

underskrift

förttydligande av underskriften

TACK FÖR ATT NI HJÄLPTE OSS!